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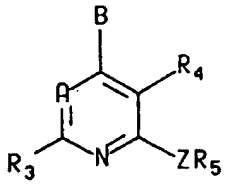
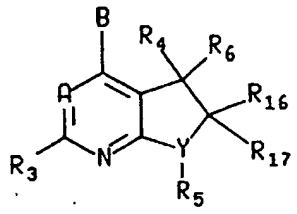
(54) Title: CORTICOTROPIN RELEASING FACTOR ANTAGONISTS

(57) Abstract

Corticotropin-releasing factor (CRF) antagonists having formulae (I), (II) or (III) wherein the dashed lines, A, B, Y, Z, G, R_3, R_4, R_5, R_6, R_{16} and R_{17} are as defined in the description, and processes for preparing them. These compounds and their pharmaceutically acceptable salts are useful in the treatment of CNS and stress-related disorders.



(I)



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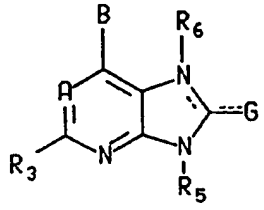

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CORTICOTROPIN RELEASING FACTOR ANTAGONISTS

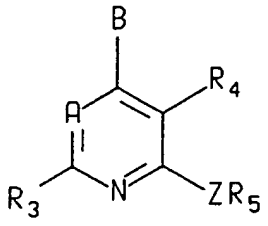
Background Of The Invention

This invention relates to pyridines, pyrimidines, purinones, pyrrolopyrimidinones and pyrrolopyridinones, processes for preparing them, pharmaceutical compositions containing them, and methods of using them to treat certain central nervous system (CNS) and other disorders.

CRF antagonists are mentioned in U.S. Patents 4,605,642 and 5,063,245 referring to peptides and pyrazolinones, respectively. The importance of CRF antagonists is set out in the literature, e.g., as discussed in U.S. Patent 5,063,245, which is incorporated herein by reference. A recent outline of the different activities possessed by CRF antagonists is found in M. J. Owens et al., Pharm. Rev., Vol. 43, pages 425 to 473 (1991), also incorporated herein by reference. Based on the research described in these two and other references, CRF antagonists are effective in the treatment of a wide range of stress-related illnesses, such as depression, anxiety, headache, irritable bowel syndrome, inflammatory diseases, immune suppression, Alzheimer's disease, gastrointestinal diseases, anorexia nervosa, hemorrhagic stress, drug and alcohol withdrawal symptoms, drug addiction, infertility, head trauma, stroke, and stress-induced infections in humans and animals.

Summary of the Invention

The present invention relates to a compound of the formula



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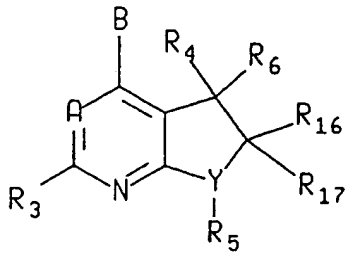

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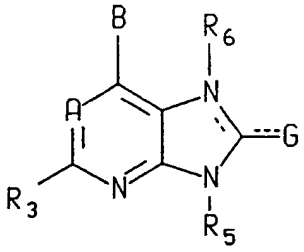


III

or a pharmaceutically acceptable salt thereof, wherein

the dashed lines represent optional double bonds;

A is $-CR_7$ or N;

B is $-NR_1R_2$, $-CR_1R_2R_{11}$, $-C(=CR_2R_{12})R_1$, $-NHCHR_1R_2$, $-OCHR_1R_2$, $-SCHR_1R_2$, $-CHR_2OR_{12}$, $-CHR_2SR_{12}$, $-C(S)R_2$ or $-C(O)R_2$;

G is oxygen, sulfur, NH, NCH_3, hydrogen, methoxy, ethoxy, trifluoromethoxy, methyl, ethyl, thiomethoxy, NH_2, $NHCH_3$, $N(CH_3)_2$ or trifluoromethyl;

Y is -CH or N;

Z is NH, O, S, $-N(C_1\text{-}C_2$ alkyl) or $-C(R_{13}R_{14})$, wherein R_{13} and R_{14} are each, independently, hydrogen, trifluoromethyl or methyl, or one of R_{13} and R_{14} is cyano and the other is hydrogen or methyl;

R_1 is C_1-C_6 alkyl which may optionally be substituted with one or two substituents R_8 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, CF_3, C_1-C_4 alkoxy, -O-CO-(C_1-C_4 alkyl), -O-CO-NH(C_1-C_4 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -NH(C_1-C_4 alkyl), -N(C_1-C_2 alkyl)(C_1-C_4 alkyl), -S(C_1-C_4 alkyl), -N(C_1-C_4alkyl)CO(C_1-C_4 alkyl), -NHCO(C_1-C_4 alkyl), -COO(C_1-C_4 alkyl), -CONH(C_1-C_4 alkyl), -CON(C_1-C_4 alkyl)(C_1-C_2 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl) and -SO_2(C_1-C_4 alkyl), and wherein said C_1-C_6 alkyl and the (C_1-C_4)alkyl moieties in the foregoing R_1 groups may optionally contain one carbon-carbon double or triple bond;

R_2 is C_1-C_{12} alkyl, aryl or -(C_1-C_4 alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or -(C_1-C_6 alkylene)cycloalkyl, wherein one or two of the ring carbons of said cycloalkyl having at least 4 ring members and the cycloalkyl moiety of said -(C_1-C_6 alkylene)cycloalkyl having at least 4 ring members may optionally be replaced by an oxygen or sulfur atom or by N-R_9 wherein R_9 is hydrogen or C_1-C_4 alkyl; and wherein each of the foregoing R_2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro and C_1-C_4 alkyl, or with one substituent selected from bromo, iodo, C_1-C_6 alkoxy, -O-CO-(C_1-C_6 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_6 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl), and -SO_2(C_1-C_4 alkyl), and wherein said C_1-C_{12} alkyl and the C_1-C_4 alkylene moiety of said -(C_1-C_4 alkylene)aryl may optionally contain one carbon-carbon double or triple bond;

or -NR_1R_2 or -$CR_1R_2R_{11}$ may form a saturated 5- to 8-membered carbocyclic ring which may optionally contain one or two carbon-carbon double bonds and in which one or two of the ring carbons may optionally be replaced by an oxygen or sulfur atom;

R_3 is methyl, ethyl, fluoro, chloro, bromo, iodo, cyano, methoxy, OCF_3, methylthio, methylsulfonyl, CH_2OH, or CH_2OCH_3;

R_4 is hydrogen, C_1-C_4 alkyl, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, trifluoromethoxy, -CH_2OCH_3, -$CH_2OCH_2CH_3$, -$CH_2CH_2OCH_3$, -CH_2OF_3, CF_3, amino, nitro, -NH(C_1-C_4 alkyl), -N(CH_3)$_2$, -NHCOCH$_3$, -NHCONHCH$_3$, -SO_n(C_1-C_4 alkyl) wherein n is 0, 1 or 2, cyano, hydroxy, -CO(C_1-C_4 alkyl), -CHO, cyano or -COO(C_1-C_4 alkyl) wherein said C_1-C_4 alkyl may optionally contain one double or triple bond and may optionally be substitut d with one substituent selected from hydroxy, amino, -NHCOCH$_3$, -NH(C_1-

C_2 alkyl), -N(C_1-C_2 alkyl)$_2$, -COO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, chloro, cyano and nitro;

R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, furanyl, benzofuranyl, benzothiazolyl, or indolyl, wherein each of the above groups R_5 is substituted with from one to three substituents independently selected from fluoro, chloro, C_1-C_6 alkyl, and C_1-C_6 alkoxy, or with one substituent selected from hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, -(C_1-C_6 alkyl)O(C_1-C_6)alkyl, -$NHCH_3$, -$N(CH_3)_2$, -COOH, -COO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl), -SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SO_2NH_2, -NHSO_2(C_1-C_4 alkyl), -S(C_1-C_6 alkyl) and -SO_2(C_1-C_6 alkyl), and wherein the C_1-C_4 alkyl and C_1-C_6 alkyl moieties of the foregoing R_5 groups may optionally be substituted with one or two fluoro groups or with one substituent selected from hydroxy, amino, methylamino, dimethylamino and acetyl;

R_6 is hydrogen or C_1-C_6 alkyl, wherein said C_1-C_6 alkyl may optionally be substituted with one hydroxy, methoxy, ethoxy or fluoro group;

R_7 is hydrogen, methyl, fluoro, chloro, bromo, iodo, cyano, hydroxy, -O(C_1-C_4 alkyl), -C(O)(C_1-C_4 alkyl), -C(O)O(C_1-C_4 alkyl), -OCF_3, CF_3, -CH_2OH, -CH_2OCH_3 or -$CH_2OCH_2CH_3$;

R_{11} is hydrogen, hydroxy, fluoro, or methoxy;

R_{12} is hydrogen or C_1-C_4 alkyl; and

R_{16} and R_{17} are each, independently, hydrogen, hydroxy, methyl, ethyl, methoxy, or ethoxy, except that R_{16} and R_{17} are not both methoxy or ethoxy;

or R_{16} and R_{17} together form an oxo (=O) group;

with the proviso that when G is oxygen, sulfur, NH or NCH_3, it is double bonded to the five membered ring of structure III, and with the further proviso that R_6 is absent when the nitrogen to which it is attached is double bonded to an adjacent ring carbon atom.

More specific embodiments of this invention include compounds of the formula I, II or III wherein: (a) B is -NR_1R_2, -$NHCHR_1R_2$, -$SCHR_1R_2$ or -$OCHR_1R_2$; R_1 is C_1-C_6 alkyl, which may optionally be substituted with one hydroxy, fluoro, CF_3, or C_1-C_2 alkoxy group and may optionally contain one double or triple bond; and R_2 is benzyl or C_1-C_6 alkyl which may optionally contain one carbon-carbon double or triple bond, wherein said C_1-C_6 alkyl or the phenyl moiety of said benzyl may optionally be substituted with fluoro, CF_3, C_1-C_2 alkyl, or C_1-C_2 alkoxy; or (b) B is -$CR_1R_2R_{11}$ wherein R_1 is C_1-C_6 alkyl

which may optionally be substituted with one C_1-C_2 alkoxy, CF_3, fluoro or hydroxy group; R_2 is benzyl or C_1-C_6 alkyl wherein said C_1-C_6 alkyl or the phenyl moiety of said benzyl may optionally be substituted with one C_1-C_2 alkyl, CF_3, C_1-C_2 alkoxy, fluoro, chloro or bromo group; and R_{11} is hydrogen or fluoro.

Other more specific embodiments of this invention include compounds of the formula I, II or III wherein R_1 is C_1-C_6 alkyl which may optionally be substituted by fluoro, CF_3, hydroxy, C_1-C_2 alkyl or C_1-C_2 alkoxy and may optionally contain one carbon-carbon double or triple bond, and R_2 is C_1-C_4 alkyl which may optionally be substituted with fluoro, chloro, CF_3, C_1-C_4 alkyl or C_1-C_4 alkoxy.

Other more specific embodiments of this invention include compounds of the formula I, II or III wherein R_3 is methyl, chloro, or methoxy, R_4 is methyl, $-CH_2OH$, cyano, trifluoromethoxy, methoxy, trifluoromethyl, chloro, $-COOCH_3$, $-CH_2OCH_3$, $-CH_2Cl$, $-CH_2F$, amino or nitro; R_6 is hydrogen, methyl or ethyl and R_5 is phenyl or pyridyl wherein said phenyl or pyridyl is substituted by two or three substituents independently selected from fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, trifluoromethyl, C_1-C_6 alkyl which may optionally be substituted with one hydroxy, C_1-C_2 alkoxy or fluoro group and may optionally contain one carbon-carbon double or triple bond, -(C_1-C_4 alkylene)O(C_1-C_2 alkyl), C_1-C_3 hydroxyalkyl, hydroxy, formyl, -COO(C_1-C_2 alkyl), -(C_1-C_2 alkylene)amino, and -(C(O)(C_1-C_4 alkyl).

Examples of preferred compounds of this invention are:

4-(1-ethyl-propoxy)-2,5-dimethyl-6-(2,4,6-trimethyl-benzyl)-pyrimidine;

2-(4-bromo-2,6-dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine;

2-(4-ethyl-2,6-dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine;

3-ethyl-4-(1-ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridine;

2-(2,6-dimethyl-4-propyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine;

4-(1-ethyl-propoxy)-2-(4-methoxy-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridine;

2-(4-ethoxy-2,6-dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine;

2-(4-chloro-2,6-dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine;

4-(1-methoxymethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine;

[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-diethyl-amine;

[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-ethyl-propyl-amine;

[2,5-dimethyl-6-(2,4,6-trimethyl-phenoxy)-pyrimidin-4-yl](1-ethyl-propyl)-amin ;

butyl-[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-ethyl-amine;

4-(1-ethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethyl-phenylsulfanyl)-pyridine;

butyl-[2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-ethyl-amine;

4-(1-ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic acid methyl ester;

[3,6-dimethyl-[2-(2,4,6-trimethyl-phenylsulfanyl)-pyridin-4-yl]-ethyl-propyl-amine;

4-(1-ethyl-propylamino)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-3-yl]-methanol;

[2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-ethyl-propyl-amine;

1-(ethyl-propyl)-[6-methyl-3-nitro-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-amine;

N4-(1-ethyl-propyl)-6-methyl-3-nitro-N2-(2,4,6-trimethyl-phenyl)-pyridine-2,4-diamine;

N4-(1-ethyl-propyl)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridine-3,4-diamine;

3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-ethyl-(2,2,2-trifluoro-ethyl)-amine;

N4-(1-ethyl-propyl)-6-methyl-N2-(2,4,6-trimethyl-phenyl)-pyridine-2,3,4-triamine;

[3-chloromethyl-6-methyl-2-(2,4,6-trimethyl-phenoxy)pyridin-4-yl]-(1-ethyl-propyl)-amine;

[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-(1-ethyl-propyl)-amine;

(1-ethyl-propyl)-[2-methyl-5-nitro-6-(2,4,6-trimethyl-pyridin-3-yloxy)-pyrimidin-4-yl]-amine;

(1-ethyl-propyl)-[3-methoxymethyl-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-amine;

(N-(1-ethyl-propyl)-2-methyl-5-nitro-N'-(2,4,6-trimethyl-pyridin-3-yl)-pyrimidine-4,6-diamine;

[2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-diethyl-amine;

4-(1-ethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethylphenoxy)-pyridine;

butyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl]-ethyl-amine;

4-(butyl-ethylamino)-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one;

4-(1-ethylpropoxy)-2,5-dimethyl-6-(2,4,6-trimethylphenoxy)-pyrimidine;

N-butyl-N-ethyl-2,5-dimethyl-N'-(2,4,6-trimethylphenyl)-pyrimidine-4,6-diamine;

(1-ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-imidazo[4,5-b]pyridin-7-yl]-amine;

[2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-3H-imidazo[4,5-b]pyridin-7-yl]-(1-ethyl-propyl)-amine;

N4-(1-ethyl-propyl)-6,N3-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine-3,4-diamine;

N4-(1-ethyl-propyl)-6,N3,N3-trimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine-3,4-diamine;

6-(1-ethyl-propoxy)-2-methyl-N4-(2,4,6-trimethyl-phenyl)-pyrimidine-4,5-diamine;

[4-(1-ethyl-propoxy)-3,6-dimethyl-pyridin-2-yl]-(2,4,6-trimethylphenyl)-amine; and

6-(ethyl-propyl-amino)-2,7-dimethyl-9-(2,4,6-trimethylphenyl)-7,9-dihydro-purin-8-one.

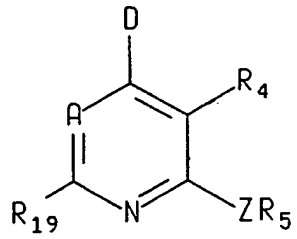
The invention also relates to a pharmaceutical composition for the treatment of (a) a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitated by CRF, or (b) a disorder selected from inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic; phobias; obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, single episode depression, recurrent depression, child abuse induced depression, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome, Crohn's disease; spastic colon; human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; chemical dependencies and addictions (e.g., dependencies on alcohol, cocaine, heroin, benzodiazepines, or other drugs); drug and alcohol withdrawal symptoms; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiarrhetic hormone (ADH); obesity; infertility; head traumas; spinal cord trauma; ischemic neuronal damage (e.g., cerebral ischemia such as cerebral hippocampal ischemia); excitotoxic neuronal damage; epilepsy; stroke; immune dysfunctions including stress induced immune

dysfunctions (e.g., porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, and dysfunctions induced by confinement in chickens, sheering stress in sheep or human-animal interaction related stress in dogs); muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; and hypoglycemia in a mammal, including a human, comprising an amount of a compound of the formula I, II or III, or a pharmaceutically acceptable salt thereof, that is effective in the treatment of such disorder, and a pharmaceutically acceptable carrier.

The invention further includes a method for the treatment of (a) a disorder the treatment of which can be effected or facilitated by antagonizing CRF, including but not limited to disorders induced or facilitator by CRF, or (b) a disorder selected from inflammatory disorders such as rheumatoid arthritis and osteoarthritis, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic; phobias; obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception such as fibromyalgia; mood disorders such as depression, including major depression, single episode depression, recurrent depression, child abuse induced depression, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome; Crohn's disease; spastic colon; human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Huntington's disease; gastrointestinal diseases; eating disorders such as anorexia and bulimia nervosa; hemorrhagic stress; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiarrhetic hormone (ADH); obesity; infertility; head traumas; spinal cord trauma; ischemic neuronal damage (e.g., cerebral ischemia such as cerebral hippocampal ischemia); excitotoxic neuronal damage; epilepsy; stroke; immune dysfunctions including stress induced immune dysfunctions (e.g., porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, and dysfunctions induced by confinement in chickens, sheering stress in sheep or human-animal interaction related stress in dogs); muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multiinfarct dementia; amyotrophic lateral sclerosis; chemical dependencies and addictions (e.g., dependencies on alcohol, cocaine, heroin, benzodiazepines, or other drugs); drug and alcohol withdrawal symptoms; and hypoglycemia in a mammal, including a human,

comprising administering to a subject in need of said treatment an amount of a compound of the formula I, II or III or a pharmaceutically acceptable salt thereof, that is effective in treating such disorder.

The invention further includes intermediate compounds of formula



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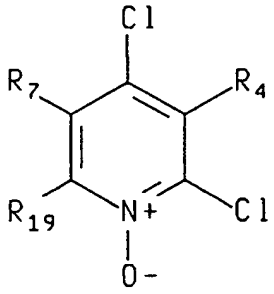
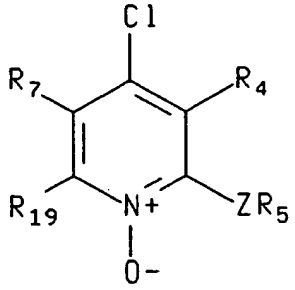


XI

and

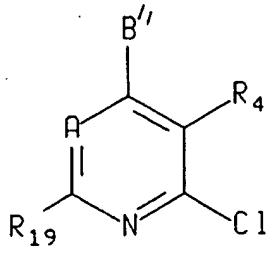


X

wherein R_4 and R_7 are defined as they are for formula I above; D is chloro, hydroxy or cyano; R_{19} is methyl or ethyl; R_5 is phenyl or pyridyl and R_5 is substituted by two or three substituents independently selected from C_1-C_4 alkyl, chloro and bromo, except that no more than one such substituent can be bromo; A is N, CH or CCH_3; and Z is O, NH, $N(CH_3)$, S or CH_2, with the proviso that when A is CH or CCH_3, then Z must be O or S.

More specific embodiments of this invention relate to compounds of the formula X or XI wherein R_7 is hydrogen or methyl.

This invention further include intermediate compounds of formula

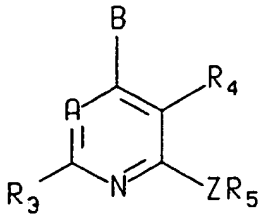


XII

wherein R_{19} is methyl or ethyl; A is N, CH or CCH_3; and wherein when A is N, then B'' and R_4 are defined, respectively, as B and R_4 are defined for formula I, and when A is CH or CH_3, then B'' is $-NR_1R_2$, $-NHR_1R_2$, $-OCHR_1R_2$ or cyano and R_4 is an electron deficient group such as NO_2, $-COO(C_1-C_4$ alkyl), $-C(=O)CH_3$, -COOH or CN.

A more specific embodiment of this invention relates to compounds of the formula XII wherein B'' is $-NR_1R_2$ or $-NHCHR_1R_2$ and A is CH or CH_3.

This invention also relates to a process for preparing a compound of the formula I,



I

or a pharmaceutically acceptable salt thereof, wherein

A is $-CR_7$ or N;

B is $-NR_1R_2$, $-NHCHR_1R_2$, $-OCHR_1R_2$ or $-SCHR_1R_2$;

Z is NH, O, S, -N(C_1-C_2 alkyl) or -C($R_{13}R_{14}$), wherein R_{13} and R_{14} are each, independently, hydrogen, trifluoromethyl or methyl, or one of R_{13} and R_{14} is cyano and the other is hydrogen or methyl;

R_1 is C_1-C_6 alkyl which may optionally be substituted with one or two substituents R_8 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, CF_3 and C_1-C_4 alkoxy, and wherein said C_1-C_6 alkyl and the (C_1-C_4)alkyl moiety of said C_1-C_4 alkoxy may optionally contain one carbon-carbon double or triple bond;

R_2 is C_1-C_{12} alkyl, aryl or -(C_1-C_4 alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or -(C_1-C_6 alkylene)cycloalkyl, wherein one or two of the ring carbons of said cycloalkyl having at least 4 ring members and the cycloalkyl moiety of said -(C_1-C_6 alkylene)cycloalkyl having at least 4 ring members may optionally be replaced by an oxygen or sulfur atom or by N-R_9 wherein R_9 is hydrogen or C_1-C_4 alkyl; and wherein each of the foregoing R_2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro and C_1-C_4 alkyl, or with one substituent selected from bromo, iodo, C_1-C_6 alkoxy, -O-CO-(C_1-C_6 alkyl), -O-CO-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -S(C_1-C_6 alkyl), CN, NO_2, -SO(C_1-C_4 alkyl), and -SO_2(C_1-C_4 alkyl), and wherein said C_1-C_{12} alkyl and the C_1-C_4 alkylene moiety of said -(C_1-C_4 alkylene)aryl may optionally contain one carbon-carbon double or triple bond;

or -NR_1R_2 may form a saturated 5- to 8-membered carbocyclic ring which may optionally contain one or two carbon-carbon double bonds and in which one or two of the ring carbons may optionally be replaced by an oxygen or sulfur atom;

R_3 is methyl or ethyl;

R_4 is hydrogen, C_1-C_4 alkyl, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, trifluoromethoxy, -CH_2OCH_3, -$CH_2OCH_2CH_3$, -$CH_2CH_2OCH_3$, -CH_2OF_3, CF_3, amino, nitro, -NH(C_1-C_4 alkyl), -N(CH_3)$_2$, -NHCOCH$_3$, -NHCONHCH$_3$, -SO_n(C_1-C_4 alkyl) wherein n is 0, 1 or 2, cyano, hydroxy, -CO(C_1-C_4 alkyl), -CHO, cyano or -COO(C_1-C_4 alkyl) wherein said C_1-C_4 alkyl may optionally contain one double or triple bond and may optionally be substituted with one substituent selected from hydroxy, amino, -NHCOCH$_3$, -NH(C_1-

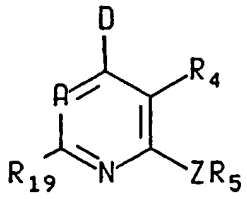
C_2 alkyl), -N(C_1-C_2 alkyl)$_2$, -COO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, chloro, cyano and nitro;

R_5 is phenyl or pyridyl, and R_5 is substituted with from one to three substituents independently selected from fluoro, chloro, C_1-C_6 alkyl, and C_1-C_6 alkoxy, or with one substituent selected from hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, -(C_1-C_6 alkyl)O(C_1-C_6)alkyl, -NHCH$_3$, -N(CH$_3$)$_2$, -COOH, -COO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -SO$_2$NH(C_1-C_4 alkyl), -SO$_2$N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SO$_2$NH$_2$, -NHSO$_2$(C_1-C_4 alkyl), -S(C_1-C_6 alkyl) and -SO$_2$(C_1-C_6 alkyl), and wherein the C_1-C_4 alkyl and C_1-C_6 alkyl moieties of the foregoing R_5 groups may optionally be substituted with one or two fluoro groups or with one substituent selected from hydroxy, amino, methylamino, dimethylamino and acetyl; and

R_7 is hydrogen or methyl;

or a pharmaceutically acceptable salt of such compound;

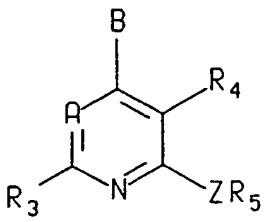
comprising reacting a compound of the formula



IV

wherein R_{19} is methyl or ethyl, D is chloro and A, Z, R_4 and R_5 are defined as above, with a compound of the formula BH, wherein B is defined as above, in the presence of a base; and then optionally converting the compound of formula I formed in such reaction into a pharmaceutically acceptable salt.

This invention also relates to a process for preparing a compound of the formula



I

or a pharmaceutically acceptable salt thereof, wherein

A is $-CR_7$ or N;

B is $-NR_1R_2$, $-CR_1R_2R_{11}$, $-C(=CR_2R_{12})R_1$, $-NHCHR_1R_2$, $-OCHR_1R_2$, $-SCHR_1R_2$, $-CHR_2OR_{12}$, $-CHR_2SR_{12}$, $-C(S)R_2$ or $-C(O)R_2$;

Z is NH, O, S, $-N(C_1-C_2$ alkyl) or $-C(R_{13}R_{14})$, wherein R_{13} and R_{14} are each, independently, hydrogen, trifluoromethyl or methyl, or one of R_{13} and R_{14} is cyano and the other is hydrogen or methyl;

R_1 is C_1-C_6 alkyl which may optionally be substituted with one or two substituents R_8 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, CF_3 and C_1-C_4 alkoxy, and wherein said C_1-C_6 alkyl and the (C_1-C_4)alkyl moiety of said C_1-C_4 alkoxy may optionally contain one carbon-carbon double or triple bond;

R_2 is C_1-C_{12} alkyl, aryl or $-(C_1-C_4$ alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or $-(C_1-C_6$ alkylene)cycloalkyl, wherein one or two of the ring carbons of said cycloalkyl having at least 4 ring members and the cycloalkyl moiety of said $-(C_1-C_6$ alkylene)cycloalkyl having at least 4 ring members may optionally be replaced by an oxygen or sulfur atom or by N-R_9 wherein R_9 is hydrogen or C_1-C_4 alkyl; and wherein each of the foregoing R_2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro and C_1-C_4 alkyl, or with one substituent selected from bromo, iodo, C_1-C_6 alkoxy, $-O-CO-(C_1-C_6$ alkyl), $-O-CO-N(C_1-C_4$ alkyl)(C_1-C_2 alkyl), $-S(C_1-C_6$ alkyl), CN, NO_2, $-SO(C_1-C_4$ alkyl), and $-SO_2(C_1-C_4$ alkyl), and wherein

said C_1-C_{12} alkyl and th C_1-C_4 alkylene moiety of said -(C_1-C_4 alkylene)aryl may optionally contain one carbon-carbon double or triple bond;

or -NR_1R_2 may form a saturated 5- to 8-membered carbocyclic ring which may optionally contain one or two carbon-carbon double bonds and in which one or two of the ring carbons may optionally be replaced by an oxygen or sulfur atom;

R_3 is methyl, ethyl, fluoro, chloro, bromo, iodo, cyano, methoxy, OCF_3, methylthio, methylsulfonyl, CH_2OH, or CH_2OCH_3;

R_4 is hydrogen, C_1-C_4 alkyl, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, trifluoromethoxy, -CH_2OCH_3, -$CH_2OCH_2CH_3$, -$CH_2CH_2OCH_3$, -CH_2OF_3, CF_3, amino, nitro, -NH(C_1-C_4 alkyl), -$N(CH_3)_2$, -$NHCOCH_3$, -$NHCONHCH_3$, -SO_n(C_1-C_4 alkyl) wherein n is 0, 1 or 2, cyano, hydroxy, -CO(C_1-C_4 alkyl), -CHO, cyano or -COO(C_1-C_4 alkyl) wherein said C_1-C_4 alkyl may optionally contain one double or triple bond and may optionally be substituted with one substituent selected from hydroxy, amino, -$NHCOCH_3$, -NH(C_1-C_2 alkyl), -$N(C_1$-C_2 alkyl)$_2$, -COO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, chloro, cyano and nitro;

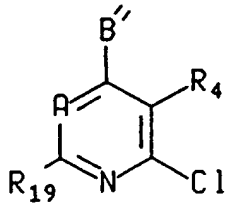
R_5 is phenyl or pyridyl and R_5 is substituted with from one to three substituents independently selected from fluoro, chloro, C_1-C_6 alkyl, and C_1-C_6 alkoxy, or with one substituent selected from hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, -(C_1-C_6 alkyl)O(C_1-C_6)alkyl, -$NHCH_3$, -$N(CH_3)_2$, -COOH, -COO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -SO_2NH(C_1-C_4 alkyl), -$SO_2N(C_1$-C_4 alkyl)(C_1-C_2 alkyl), -SO_2NH_2, -$NHSO_2$(C_1-C_4 alkyl), -S(C_1-C_6 alkyl) and -SO_2(C_1-C_6 alkyl), and wherein the C_1-C_4 alkyl and C_1-C_6 alkyl moieties of the foregoing R_5 groups may optionally be substituted with one or two fluoro groups or with one substituent selected from hydroxy, amino, methylamino, dimethylamino and acetyl; and

R_7 is hydrogen or methyl;

with the proviso that when A is CH or CCH_3, then R_4 is an electron deficient group such as NO_2, -COO(C_1-C_4)alkyl, -C(=O)CH_3, -COOH or CN;

or a pharmaceutically acceptable salt of such compound;

comprising reacting a compound of the formula

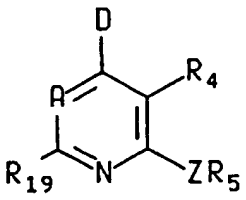


XII

wherein R_{19} is methyl or ethyl and A is N, CH or CCH_3; and wherein when A is N, then B'' and R_4 are defined, respectively, as B and R_4 are defined in claim 1, and when A is CH or CH_3, then B'' is $-NR_1R_2$, $-NHR_1R_2$, $-OCHR_1R_2$ or cyano and R_4 is an electron deficient group such as NO_2, $-COO(C_1-C_4$ alkyl), $-C(=O)CH_3$, -COOH or CN;

with a compound of the formula R_5ZH, wherein R_5 and Z are defined as above, and then optionally converting the compound of formula I formed by such reaction into a pharmaceutically acceptable salt.

This invention also relates to a process for preparing a compound of the formula



IV

a wherein R_{19} is methyl or ethyl;

D is chloro;

A is $-CR_7$ or N;

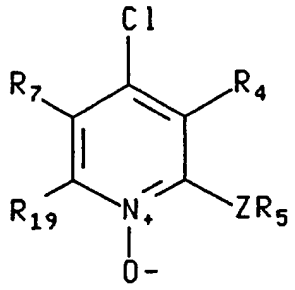
Z is NH, O, S, $-N(C_1-C_2$ alkyl) or $-C(R_{13}R_{14})$, wherein R_{13} and R_{14} are each, independently, hydrogen, trifluoromethyl or methyl, or one of R_{13} and R_{14} is cyano and the other is hydrogen or methyl;

R_4 is hydrogen, C_1-C_4 alkyl, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, trifluoromethoxy, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OCH_3$, $-CH_2OF_3$, CF_3, amino, nitro, $-NH(C_1-C_4$ alkyl), $-N(CH_3)_2$, $-NHCOCH_3$, $-NHCONHCH_3$, $-SO_n(C_1-C_4$ alkyl) wherein n is 0, 1 or 2, cyano, hydroxy, $-CO(C_1-C_4$ alkyl), -CHO, cyano or $-COO(C_1-C_4$ alkyl) wherein said C_1-C_4 alkyl may optionally contain one double or triple bond and may optionally

be substituted with one substituent selected from hydroxy, amino, -NHCOCH$_3$, -NH(C_1-C_2 alkyl), -N(C_1-C_2 alkyl)$_2$, -COO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, chloro, cyano and nitro; and

R_5 is phenyl or pyridyl, and R_5 is substituted with from one to three substituents independently selected from fluoro, chloro, C_1-C_6 alkyl, and C_1-C_6 alkoxy, or with one substituent selected from hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, -(C_1-C_6 alkyl)O(C_1-C_6)alkyl, -NHCH$_3$, -N(CH$_3$)$_2$, -COOH, -COO(C_1-C_4 alkyl), -CO(C_1-C_4 alkyl), -SO$_2$NH(C_1-C_4 alkyl), -SO$_2$N(C_1-C_4 alkyl)(C_1-C_2 alkyl), -SO$_2$NH$_2$, -NHSO$_2$(C_1-C_4 alkyl), -S(C_1-C_6 alkyl) and -SO$_2$(C_1-C_6 alkyl), and wherein the C_1-C_4 alkyl and C_1-C_6 alkyl moieties of the foregoing R_5 groups may optionally be substituted with one or two fluoro groups or with one substituent selected from hydroxy, amino, methylamino, dimethylamino and acetyl;

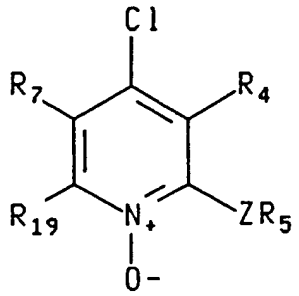
comprising reacting a compound of the formula



X

wherein R_{19}, R_4 and R_5 are defined as above and R_7 is hydrogen, methyl, fluoro, chloro, bromo, iodo, cyano, hydroxy, -O(C_1-C_4 alkyl), -C(O)(C_1-C_4 alkyl), -C(O)O(C_1-C_4 alkyl), -OCF$_3$, CF$_3$, -CH$_2$OH, -CH$_2$OCH$_3$ or -CH$_2$OCH$_2$CH$_3$, with phorphorus trichloride.

This invention also relates to a process for preparing a compound of the formula



X

wherein R_{19} is methyl or ethyl;

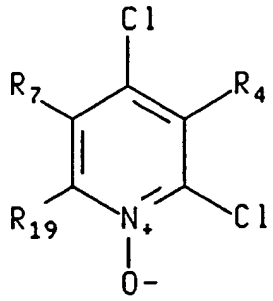
A is $-CR_7$ or N;

Z is O, S, or $-C(R_{13}R_{14})$, wherein R_{13} and R_{14} are each, independently, hydrogen, trifluoromethyl or methyl, or one of R_{13} and R_{14} is cyano and the other is hydrogen or methyl;

R_4 is hydrogen, C_1-C_4 alkyl, fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, trifluoromethoxy, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OCH_3$, $-CH_2OF_3$, CF_3, amino, nitro, $-NH(C_1$-C_4 alkyl), $-N(CH_3)_2$, $-NHCOCH_3$, $-NHCONHCH_3$, $-SO_n(C_1$-C_4 alkyl) wherein n is 0, 1 or 2, cyano, hydroxy, $-CO(C_1$-C_4 alkyl), -CHO, cyano or $-COO(C_1$-C_4 alkyl) wherein said C_1-C_4 alkyl may optionally contain one double or triple bond and may optionally be substituted with one substituent selected from hydroxy, amino, $-NHCOCH_3$, $-NH(C_1$-C_2 alkyl), $-N(C_1$-C_2 alkyl)$_2$, $-COO(C_1$-C_4 alkyl), $-CO(C_1$-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, chloro, cyano and nitro; and

R_5 is phenyl or pyridyl, and R_5 is substituted with from one to three substituents independently selected from fluoro, chloro, C_1-C_6 alkyl, and C_1-C_6 alkoxy, or with one substituent selected from hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, $-(C_1$-C_6 alkyl)$O(C_1$-C_6)alkyl, $-NHCH_3$, $-N(CH_3)_2$, -COOH, $-COO(C_1$-C_4 alkyl), $-CO(C_1$-C_4 alkyl), $-SO_2NH(C_1$-C_4 alkyl), $-SO_2N(C_1$-C_4 alkyl)$(C_1$-C_2 alkyl), $-SO_2NH_2$, $-NHSO_2(C_1$-C_4 alkyl), $-S(C_1$-C_6 alkyl) and $-SO_2(C_1$-C_6 alkyl), and wherein the C_1-C_4 alkyl and C_1-C_6 alkyl moieties of the foregoing R_5 groups may optionally be substituted with one or two fluoro groups or with one substituent selected from hydroxy, amino, methylamino, dimethylamino and acetyl;

comprising reacting a compound of the formula



XI

wherein R_4, R_7 and R_{19} are defined as above, with a compound of the formula R_5OH or R_5SH, wherein R_5 is defined as above, in the presence of a base.

Detailed Description of the Invention

Methods of preparing the compounds and compositions of this invention are described below. In the discussion and reaction schemes that follow, R_1 through R_9, R_{11}, R_{12}, R_{16}, R_{17}, R_{19}, A, B, G, the dashed lines and structural formulae I, II, III, X, XI, XII and IV, unless otherwise indicated, are defined as above.

Whenever reference is made herein to C_1-C_6 alkyl, a straight or branched chain alkyl of one to six carbon atoms is meant, such as methyl, ethyl, isopropyl, t-butyl or hexyl.

Whenever R_2 or R_5 is a heterocyclic group, attachment of the group is through a carbon atom.

Whenever reference is made herein to C_1-C_4 alkyl or C_1-C_6 alkyl which "may contain one double or triple bond" in the definitions of R_1, R_2 and R_3, it is understood that at least two carbons are present in the alkyl for one double or triple bond.

Whenever reference is made herein to halo or halogen, fluoro, chloro, bromo or iodo is meant unless indicated otherwise.

Compounds of the formula I wherein B is $-NR_1R_2$, $-NHCHR_1R_2$, $-OCHR_1R_2$ or $-SCHR_1R_2$, and R_3 is methyl, ethyl or chloro (hereinafter R_{19}) may be prepared by reaction of a compound of the formula IV wherein D is Cl, and A, R_4, R_5, and Z are as defined above with reference to formula I, with a compound of the formula BH wherein B is as defined immediately above. The reaction is carried out in a solvent in the presence of a base at a temperature of between about 0° to about 230°C. Suitable solvents are organic solvents such as tetrahydrofuran (THF), acetonitrile,

dimethylsulfoxide (DMSO), acetone, C_2-C_{15} alkyl alcohol, chloroform ($CHCl_3$), benzene, xylene, toluene, sulfolane, pyridine, quinoline, 2,4,6-trimethylpyridine, acetamide, di-(C_1-C_2)alkylacetamide or 1-methyl-2-pyrrolidinone.

A preferred method of preparing compounds of the formula I wherein A is -CR_7 and B is -NR_1R_2 or -$NHCHR_1R_2$ is the two step procedure described below. First, a compound of the formula IV is reacted with an excess of R_1NH_2 or NH_3 or an equivalent NH_3 precursor (e.g., NaN_3, $nBu_4N^+N_3^-$ or NH_2OH) at temperature from about 75°C to about 250°C and at a pressure from about 0 to about 300 psi, in an appropriate solvent, as described above, to form a compound of the formula I wherein B is -NHR_1, -NH_2, -NH_2OH or -N_3. Compounds of the formula I wherein B is -N_3 or -NH_2OH can be converted into the corresponding compounds of formula I wherein B is -NH_2 by methods well known in the art such as hydrogenation or reduction. Alkylation of a compound of the formula I wherein B is -NHR_1 or -NH_2 with an appropriate alkyl halide in the presence of an appropriate base such as lithium or sodium bistrimethylsilylamide, lithium or sodium diisopropylamide, n-butyllithium or potassium t-butoxide, in an appropriate solvent such as THF, dioxane or methylene chloride, will yield the corresponding compound of formula I wherein B is -NR_1R_2. Alternatively, reductive amination of a compound of the formula I wherein B is -NHR_1 or -NH_2, for example, acylation, followed by reduction with a borohydride (e.g., sodium borohydride) will form the corresponding compound of formula I wherein B is -NR_1R_2 or $NHCHR_1R_2$.

When B is -NR_1R_2 or -$NHCHR_1R_2$, an excess of BH may be used both as a reagent and as a base. Bases other than BH such as potassium carbonate, tri-(C_1-C_6)alkylamine or sodium hydride may also be used. The reaction is carried out at a temperature of about 75° to 230°C. When the reaction is carried out in the presence of a base, such as sodium hydride, potassium C_1-C_4 alkoxide, or an organolithium compound such as n-butyllithium, a molar equivalent of the amine is used.

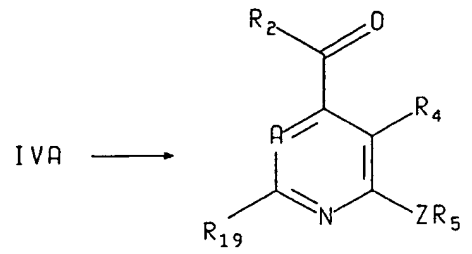
When B is -$OCHR_1R_2$ or -$SCHR_1R_2$, a base which is capable of deprotonating BH may be used, such as an alkali metal hydride such as sodium or potassium hydride, or an organometallic base such as sodium diisopropylamide, sodium bis(trimethylsilyl)amide, lithium diisopropylamide, lithium bis(trimethylsilyl)amide, sodium or potassium C_1-C_4 alkoxide, or n-butyllithium. The solvent used can be, for example, tetrahydrofuran, acetonitrile, dimethylsulfoxid , aceton , methyl ne chloride, toluene, a C_2-C_5 alcohol, chloroform, b nzen , xylene, or 1-methyl-2-pyrrolidinone, and the

reaction temperature can range from about 0°C to about 180°C, and is preferably from about 50°C to about 80°C.

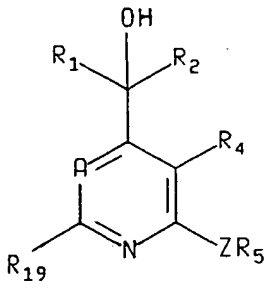
Compounds of the formulae I, II and III wherein B is as defined with reference to formulae I, II and III and R_3 is defined with reference to the same except that R_3 is not methyl or ethyl (hereinafter R_{20}, which is defined as R_3 with the exception that it can not be methyl or ethyl) may be prepared by reacting a compound of the formulae I, II or III wherein R_3 is chloro with a nucleophile of the formula $R_{20}H$ with or without an organic or inorganic base. Suitable bases include sodium and sodium hydride, when $R_{20}H$ is an alkanol or an alkane thiol; and weaker bases such as potassium carbonate or triethylamine when $R_{20}H$ is an amine. The compounds of formula I wherein R_{20} is fluoro may be prepared from the corresponding compounds wherein R_{20} is chloro on reaction with tetrabutylammonium fluoride. Suitable solvents are dimethylsulfoxide, tetrahydrofuran, or methylene chloride, preferably tetrahydrofuran.

Compounds of the formula I wherein B is $-CR_1R_2R_{11}$, $-C(C=CR_2R_{12})R_1$, $-CHR_2OR_{12}$, $-CHR_2SR_{12}$, or $-C(O)R_2$, and R_3 is R_{19}, as defined above, may be prepared as depicted in Scheme I.

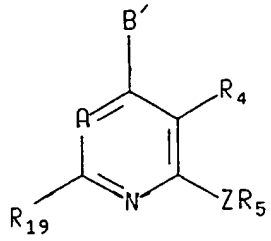
SCHEME 1



IA



IB

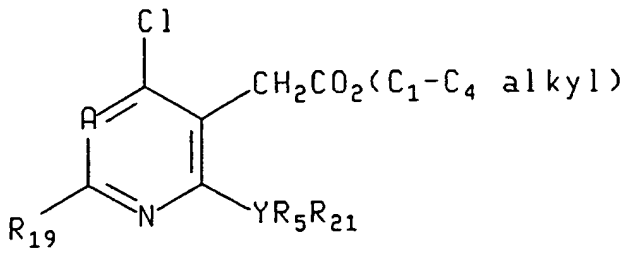


IC

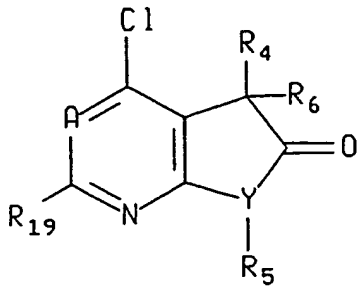
Compounds of the formula IV wherein D is cyano and A, R_4, R_5, and R_{19} are as defined above having formula IVA (not shown), prepared by reacting the corresponding compound wherein D is chloro with potassium cyanide or copper cyanide in dimethylsulfoxide, 1-methyl-2-pyrrolidinone, N,N-dimethylformamide (DMF) or acetamide, are reacted with a Grignard reagent containing group R_2, as defined above, to form the compounds of formula IA. Further reaction of the compound of formula IA with a Grignard reagent containing R_1 as defined above provides the compound of formula IB. Corresponding compounds of formula IC wherein B′ is $-CR_1R_2R_{11}$, or $-C(C=CR_2R_{12})R_1$ may be prepared by conventional methods. Thus, reaction of IB with an acid, such as concentrated sulfuric acid in acetic acid, or Burgess inner salt, such as (carboxysulfamoyl)triethylammonium hydroxide methyl ester, gives a compound of formula IC wherein B′ is $-C(=CR_2R_{12})R_1$. Hydrogenation of a compound wherein B′ is $-C(=CR_2R_{12})R_1$ using a palladium/carbon (Pd/C) or platinum dioxide catalyst gives a compound IC wherein B′ is CHR_1R_2. Reaction of compound IB with diethylaminosulfur trifluoride or triphenylphosphine/carbontetrachloride affords a compound IC wherein B′ is $-CR_1R_2F$ or $-CR_1R_2Cl$, respectively. Reduction of a compound of formula IA with sodium borohydride gives a compound I wherein B is $-CHR_2OH$. Alkylation of this $-CHR_2OH$ group with alkyl halide such as alkyl iodide in the presence of a base such as sodium hydride at room temperature affords a compound of formula I wherein B is $-CHR_2OR_{12}$.

Compounds of the formula II wherein R_3 is R_{19} as defined above may be prepared from compounds of the formula IV wherein R_{19}, R_4, R_5 and A are as defined before, D is chloro, and YR_{21} is NH or $-CHR_{21}$ wherein R_{21} is cyano or $-COO(C_1-C_4$ alkyl), hereafter formula IVB, as shown in Scheme 2.

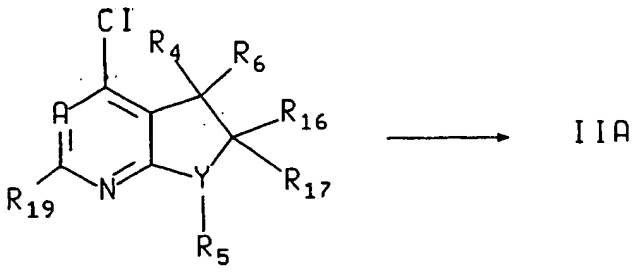
SCHEME 2



IVB



VII



VIII

Compounds of the formula VII wherein R_4 and R_6 are each hydrogen and Y is N may be prepared by heating compounds of formula IVB with an acid catalyst in a suitable solvent such as toluene, benzene, t-butanol, acetonitrile and acetone, preferably toluene. The acid catalyst may be sulfuric acid, hydrochloric acid, p-toluene sulfonic acid, or methylsulfonic acid, preferably p-toluene sulfonic acid.

When Y in formula IVB is CH or N, a base may be used to deprotonate the proton of the compound of formula IVB. Suitable solvents are tetrahydrofuran, toluene, and methylene chloride, suitable reaction temperatures are between about -78°C and 100°C, preferably -78° to 50°C, and suitable bases are sodium hydride, potassium hydride, potassium t-butoxide, lithium bis(trimethylsilyl) amide, and lithium or sodium diisopropylamide.

Compounds of the formula VII wherein R_4 and R_6 are each hydrogen may be deprotonated with a base such as sodium hydride, or an organometallic compound such as lithium bis(trimethylsilyl)amide followed by quenching with an electrophile compound containing the group R_4, such as R_4L wherein L is a leaving group such as iodo, bromo, mesylate, tosylate or with p-tolyl-N-fluoro-N-C_1-C_6 alkyl sulfonamide, iodine, p-nitrobenzene, dimethylformamide, di(C_1-C_4 alkyl)ketone, formaldehyde, (C_1-C_4 alkyl) aldehyde or bromine, to provide a compound of formula VII wherein R_4 is fluoro, chloro, bromo, iodo, hydroxy, C_1-C_4 alkyl, S(C_1-C_4 alkyl), CHO, CH(OH)(C_1-C_4 alkyl), C(OH)(di-C_1-C_4 alkyl) or CH_2OH. Further conventional alkylation of the hydroxy group or oxidation of the thioalkyl group leads to compounds of formula VII wherein R_4 is C_1-C_4 alkoxy and SO_n(C_1-C_4 alkyl) wherein n is 1 or 2, respectively. Oxidation of compounds of formula VII wherein R_4 is hydroxy and R_6 is hydrogen affords corresponding compounds wherein CR_4R_6 is C=O, which on reductive amination with an appropriate amine convert into corresponding compounds wherein R_4 is amino. The compounds of formula VII wherein R_4 is nitro or amino may be formed by reacting compounds of formula VII wherein R_4 and R_6 are both hydrogen with alkyl nitrite to form compounds wherein CR_4R_6 is C=NOH and oxidizing or reducing to give the compounds of formula VII wherein R_4 is nitro or amine, respectively.

Compounds of the formula VII, when one of R_4 and R_6 is hydrogen, may be converted into corresponding compounds wherein R_{16} and R_{17} are both hydrogen by reduction with a reducing agent such as lithium aluminum hydride in tetrahydrofuran. The same reduction leads to compounds wherein R_{16} is hydrogen and R_{17} is hydroxy,

when both of R_4 and R_6 are not hydrogen. Alkylation of R_{17} is hydroxy with C_1-C_4 alkyl iodide in the presence of sodium hydride gives the corresponding compound wherein R_{17} is O(C_1-C_4 alkyl). Reaction of compounds of formula VII with an organometallic compound such as di(C_1-C_6 alkyl)zinc, C_1-C_6 alkyl lithium, or C_1-C_6 alkyl magnesiumbromide affords compounds of formula VIII wherein one of R_{16} or R_{17} is C_1-C_6 alkyl and the other is hydroxy.

The conversion of compounds of formula VIII to corresponding compounds of formula IIA is by the methods described above for preparation of compounds of formula I.

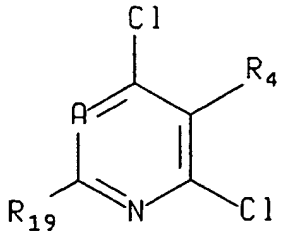
The compounds of formula III wherein G is oxygen or sulfur and R_6 is hydrogen may be prepared by reacting compounds of formula I wherein R_4 is amino and Z is NH with phosgene, diphosgene, triphosgene or thiophosgene. The reaction is in the presence of a base such as tri(C_1-C_4 alkyl)amine in a suitable solvent, preferable tetrahydrofurane at about -78°C to about 50°C, preferably at 0°C to room temperature. Standard alkylation of these compounds wherein R_6 is hydrogen with a suitable base such as sodium hydride in a suitable solvent such as dry tetrahydrofuran provides compounds of the formula III wherein R_6 is C_1-C_4 alkyl.

Compounds of the formula III wherein G is alkyl may be prepared by reacting a compound of the formula I wherein R_4 is amino and Z is NH with a compound of the formula GC(OC_1-C_2 alkyl)$_3$ in the presence of an acid such as p-toluenesulfonic acid (p-TsOH), methanesulfonic acid (MsOH), hydrogen chloride gas (HCl_g) or concentrated sulfuric acid (H_2SO_4) in an appropriate sovlent such as toluene, xylene, benzene, dioxane or THF at a tempeature from about room temperature to about 140°C, preferably from about 50°C to about the reflux temperature. Alternatively, a compound of the formula I wherein R_4 is amino and Z is NH can be reacted with $[G(C=O)]_2O$, G(C=O)Cl or G(C=O)F in the presence of a base such as pyridine, a derivative of pyridine or a tri-(C_1-C_4)alkylamine, in an appropriate solvent such as CH_2Cl_2, $CHCl_3$, THF, dioxane, toluene or benzene, at a temperature from about 0°C to about the reflux temperature of the reaction mixture, preferably from about 0°C to about room temperature, followed by ring cyclization under acidic conditions (e.g., with pTSOH, MSOH, HCl_g, hydrogen bromide gas (HBr_g) or concentrated H_2SO_4). The ring cyclization can be carried out in an appropriate solvent such as a C_1-C_6 alcohol, toluene, xylene, benzene, dioxane or THF. Suitable temperatures for this reaction can

range from about room temperature to about 140°C. Preferably, the reaction temperature is between about 50°C and about the reflux temperature.

Compounds of the formula III wherein G is -O-(C_1-C_2 alkyl) or -OCF_3 may be prepared by reacting a compound of the formula III wherein G is oxygen and R_6 is hydrogen with a compound of the formula $GOSO_2CF_3$ in the presence of a base such as tri(C_1-C_4 alkyl)amine, or with lithium bistrimethylsilylamide in HMPA or DMF, and then quenching the reaction with a compound of the formula $GOSO_2OG$ or G-X wherein X is bromo, chloro or SO_3CF_3.

The compounds of formula IV wherein D is chloro and ZR_5 is NHR_5 may be prepared from compounds of formula V:

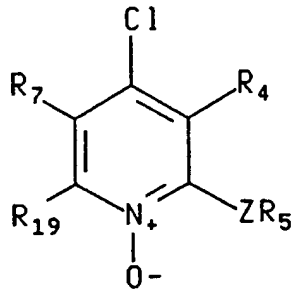


V

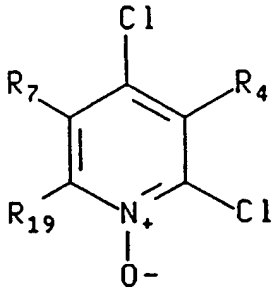
wherein A and R_4 are as defined with reference to formula I and R_{19} is as defined above, by reaction with R_5NH_2. The reaction is in tetrahydrofuran or dimethylsulfoxide at about 0°C to about 150°C, preferably 50° to 130°C. The compounds of formula IV wherein D is chloro and Z is O, S, CHR_{21}, wherein R_{21} is an electron deficient group such as cyano, C(=O)R, COOR, wherein R is C_1-C_4 alkyl, benzoyl or allyl, or SO_n-phenyl wherein n = 0, 1 or 2 may be prepared by reacting compounds of formula V with R_5OH, R_5SH, R_5NH_2 or R_5CHR_{21}. The reaction proceeds in the presence of a base which is capable of deprotonating R_5ZH, such as sodium hydride, potassium hydride, potassium carbonate, lithium or sodium bis(trimethylsilyl)amide, lithium or sodium dialkylamide, sodium or potassium (C_1-C_4 alkoxide) or n-butyllithium, with or without other organometal halides such as copper (I) bromide, iodide or chloride, copper (II) oxide, copper (I) oxide, copper metal and trialkyltinchloride. Examples of solvents that may be used are tetrahydrofuran, dimethylsulfoxide, acetonitrile, methylene chloride, 1-methyl-2-pyrrolidinone, pyridine, quinoline, N,N-dialkylacetamides, 2,4,6-trimethylpyridine, N,N-dialkylformamides, e.g., N,N-dimethylformamide (DMF),

hexamethyl phosphoramide and toluene. The reaction temperature may range from about 0°C to about 180°C, and is preferably from about 0° to about 150°C.

Compounds of the formula IV wherein A is CR_7, D is chloro and Z is O, S, CHR_{21} may be prepared by reduction of compounds of formula X, depicted below, wherein R_7 and Z are as defined immediately above, with a reducing agent such as phosphorous trichloride in an appropriate solvent such as methylene chloride or chloroform at temperature from about 0°C to about 100°C, preferably from about room temperature to about the reflux temperature of the solvent.



X



XI

Compounds of the formula X may be prepared from compounds of the formula XI, depicted above, wherein R_4 is as defined as it is for formula I and R_{19} is as defined above (i.e., methyl or ethyl), by reaction with a compound of the formula R_5OH, R_5SH or R_5CHR_{21}. This reaction proceeds in the presence of a base which is capable of deprotonating R_5ZH, such as sodium hydride, potassium hydride, lithium, sodium or potassium bis(trimethylsilyl)amide, lithium, sodium or potassium dialkylamide, sodium or potassium C_1-C_4alkoxide, or n-butyllithium. Suitable solvents include tetrahydrofuran, dioxane, dimethylsulfoxide, 1-methyl-2-pyrrolidinone, pyridine, N,N-di-(C_1-C_4 alkyl)acetamides, acetamide, N,N-di-(C_1-C_4 alkyl)formamides, acetonitrile, methylene chloride, touluene and xylene. Suitable reaction temperatures may range from about -78°C to about 150°C, and are preferably between about -40°C to about 150°C.

Compounds of the formula XI may be prepared by reacting the corresponding compounds of formula V wherein A is $-CR_7$ and R_4 and R_{19} are d fined as above, with an oxidizing agent such as m-chloroperbenzoic acid, peracetic acid or pertrifluoroacetic

acid, in a solvent such as methylene chloride, chloroform, acetic acid, DMF, methanol or a mixture of one or more of the foregoing solvents, at temperature from about 0°C to about 100°C, preferably from about room temperature to about 60°C.

When R_4 is an electron withdrawing group such as a NO_2, -COO(C_1-C_4 alkyl), -COOH, CN or -CO(C_1-C_4)alkyl, the reaction order for the coupling reactions that introduce the B and ZR_5 groups in the synthesis of compounds of formula I may be reversed. The B group may be introduced before the ZR_5 coupling step using the methods analogous to those described above. For example, compounds of the formula I wherein R_4 is an election deficient group may be prepared by reacting a compound of the formula XII with a compound of the formula HZR_5. Compounds of the formula XII may be prepared by reacting a compound of the formula V wherein A is CR_7 and R_{19} and R_4 are defined as above with a compound of the formula B''H in the presence of a base.

Compounds of the formula IV wherein D is chloro and Z is -N(C_1-C_4 alkyl) may be prepared by reacting the corresponding compounds wherein Z is NH with a base, at a temperature from about -78°C to about 100°C, preferably from about 0°C to about room temperature, followed by quenching with C_1-C_4 alkyl iodide or bromide. Suitable bases include, for example, sodium hydride, lithium or sodium bis(trimethylsilyl)amide, lithium or sodium dialkylamide, and n-butyllithium. Suitable solvents include, for example, tetrahydrofuran, dimethylsulfoxide, toluene, benzene or methylene chloride.

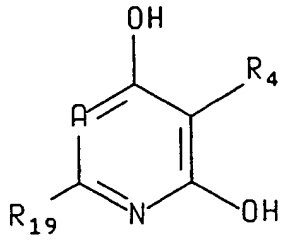
Compounds of the formula IV wherein D is chloro, hydroxy or OP wherein P is a standard protecting group for hydroxy and Z is -$CR_{13}R_{14}$ may be prepared by alkylation, using an R_{13} containing alkylating agent such as $R_{13}I$, compounds of the formula IV wherein Z is -CHR_{21} in the presence of a base that is capable of deprotonating the proton in the Z group, as mentioned above, followed by quenching with an R_{14} containing alkylating agent such as $R_{14}I$. Heating compounds of the formula IV wherein D is chloro or hydrogen and Z is -CH(CN) in about 85% phosphoric acid at about the reflux temperature yields the corresponding compounds of formula IV wherein D is hydroxy and Z is CH_2. Deprotonation of the compounds of formula IV wherein Z is CH_2 with a base, such as described above for deprotonation of R_5ZH, followed by quenching with a suitable electrophile such as a (C_1-C_6 alkyl)iodide, iodine, bromine, acetylchloride, formaldehyde, acetone, p-tolyl-N-fluoro-N-(C_1-C_6 alkyl)sulfonamide, nitrobenzene, C_1-C_6 alkylnitrit , ethylene oxide or dihaloethane yields

the corresponding compounds of formula IV wherein Z is -CHR_{13}, -CH(OH), cyclopropyl or -C(NOH). Further alkylation of compounds wherein Z is -CHR_{13}, e.g., as described immediately above, with an alkylating agent of the formula $R_{14}I$, produces the corresponding compounds wherein Z is -$C(R_{13}R_{14})$.

Conversion of -$C(R_5)$NOH or -$CH(OH)R_5$ to $C(O)R_5$ may be accomplished by known methods. Hydrogenation or reduction of compounds wherein Z is -C=NOH provides compounds wherein Z is -$CHNH_2$. Some of the intermediates may require a protecting or deprotecting procedure to control the reaction selectivity using standard organic chemistry.

Compounds of the formula V wherein A is N (hereinafter referred to as compounds of the formula VB) or A is CR_7 (i.e., compounds of the formula VA), and R_4 and R_{19} are defined as they are for formula I, may be prepared by reacting the corresponding compounds of formulae VIB and VIA, respectively, with 1 equivalent or an excess of $POCl_3$ at a temperature from about room temperature to about 180°C, preferably at the reflux temperature, with or without a solvent. Compounds of formula VIA may be prepared by the methods analogous to those described in the literature and well known to those skilled in the art. (See Helv. Chimica Acta., 25, p. 1306-1313 (1942)).

Compounds of formula VIB may be prepared by reacting 1 equivalent of the HCl salt of $R_{19}C(=NH)(NH_2)$, 1 equivalent of $R_4CH(COO\text{-}(C_1\text{-}C_2\ alkyl))_2$, and 2 equivalents of a base such as a sodium alkoxide, e.g., sodium methoxide in a mixture of an alcohol (e.g., methanol), and acetone at a temperature from about 50°C to about 200°C, preferably at the reflux temperature.



VIA, A = CR_7

VIB, A = N

When compounds of this invention contain one or more chiral centers, it is understood that the invention includes the racemic mixtures as well as all individual enantiomers and diastereomers of such compounds, and mixtures thereof.

The acid addition salts of compounds of the formulae I, II and III ("the active compounds of this invention) can be prepared in a conventional manner by treating a solution or suspension of the corresponding free base with one chemical equivalent of a pharmaceutically acceptable acid. Conventional concentration or crystallization techniques can be employed to isolate the salts. Illustrative of suitable acids are acetic, lactic, succinic, maleic, tartaric, citric, gluconic, ascorbic, benzoic, cinnamic, fumaric, sulfuric, phosphoric, hydrochloric, hydrobromic, hydroiodic, sulfamic, sulfonic acids such as methanesulfonic, benzene sulfonic, p-toluenesulfonic, and related acids.

The active compounds of this invention may be administered alone or in combination with pharmaceutically acceptable carriers, in either single or multiple doses. Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solutions and various organic solvents. The pharmaceutical compositions formed by combining the novel compounds of formulae I, II and III and their pharmaceutically acceptable carriers can then be readily administered in a variety of dosage forms such as tablets, powders, lozenges, syrups, injectable solutions and the like. These pharmaceutical compositions can, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. Thus, for purposes of oral administration, tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate may be employed along with various disintegrants such as starch, methylcellulose, alginic acid and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in soft and hard filled gelatin capsules. Preferred materials for this include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if desired, emulsifying or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin and combinations thereof.

For parenteral administration, solutions containing an active compound of this invention or a pharmaceutically acceptable salt thereof in sesame or peanut oil, aqueous propylene glycol, or in sterile aqueous solution may be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

The effective dosages for compounds of the formulae I, II or III and their salts will depend on the intended route of administration and factors such as the age and weight of the patient, as generally known to a physician. The dosages will also depend on the particular illness to be treated. For instance, the daily dosage for stress-induced illnesses, inflammatory disorders, Alzheimer's disease, gastro-intestinal diseases, anorexia nervosa, hemorrhagic stress and drug and alcohol withdrawal symptoms will generally range from about 0.1 to about 50 mg/kg body weight of the patient to be treated.

Methods that may be used to determine the CRF antagonist acivity of the active compounds of this invention and their pharmaceutically acceptable salts are described in Endocrinology, 116, 1653-1659 (1985) and Peptides, 10, 179-188 (1985). The binding activities for compounds of formulae I, II and III, expressed as IC_{50} values, generally range from about 0.5 nanomolar to about 10 micromolar.

The present invention is illustrated by the following examples. It will be understood, however, that the invention is not limited to the specific details of these examples. Melting points are uncorrected. Proton nuclear magnetic resonance spectra (^1H NMR) and C^{13} nuclear magnetic resonance spectra (C^{13} NMR) were measured for solutions in deuterochloroform ($CDCl_3$) and peak positions are expressed in parts per million (ppm) downfield from tetramethylsilane (TMS). The peak shapes are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad.

The following abbreviations are used in the Examples: Ph=phenyl; iPr=isopropyl; HRMS=high resolution mass spectrum.

Example 1

A. Butyl-(6-chloro-2,5-dimethyl-pyrimidin-4-yl)-ethylamine

A mixture of 2,5-dimethyl-4,6-dichloro-pyrimidine (0.999 g, 5.64 mmol) in 5ml of acetonitrile was treated with triethylamine (0.571 g, 5.65 mmol) and N-butyl-ethyl-amine (0.570 g, 5.65 mmol) and heated at reflux overnight. The mixture was cooled, diluted with water and dilute hydrogen chloride, and extracted with ethyl acetate. The organic layer was neutralized with saturated potassium carbonate, washed with brine, dried and concentrated to give 0.877 g (64%) of title compound as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3H), 1.15 (t, 3H), 1.22-1.36(m, 2H), 1.5-1.6(m, 2H), 2.20 (s, 3H), 2.45 (s, 3H), 3.25-3.48 (m, 4H) ppm.

B. N-Butyl-N-ethyl-2,5-dimethyl-N'-(2,4,6-trimethylphenyl)-pyrimidine-4,6-diamine

A mixture of butyl-(6-chloro-2,5-dimethyl-pyrimidin-4-yl)-ethylamine (398 mg, 1.65 mmol), 2,4,6-trimethylaniline (4.04 g, 30 mmol) and diisopropyl-ethyl-amine (200 mg, 1.55 mmol) was heated at 210 to 230°C overnight. The mixture was quenched with water and dilute hydrogen chloride, and extracted with ethyl acetate. The organic layer was neutralized with saturated potassium carbonate, washed with brine, dried and concentrated to give a dark oil. The oil was distilled to give 579 mg of dark oil which was then purified through silica gel column chromatography using 1:1 hexane to chloroform as eluent to give 327 mg of title compound as a yellow solid. ^{1}H NMR ($CDC1_3$) δ 0.92 (t, 3H), 1.14 (t, 3H), 1.2-1.4 (m, 2h), 1.45-1.60 (m, 2H), 1.85 (s, 3H), 2.16 (s, 6H), 2.30 (s, 3H), 2.33 (s, 3H), 3.2-3.4 (m, 4H), 5.8 (brs, 1H), 6.90 (s, 2H) ppm.

Example 2

A. Butyl-(6-chloro-2-methyl-pyrimidin-4-yl)-ethylamine

A mixture of 2-methyl-4,6-dichloro-pyrimidine (1.63 g, 10 mmol) in 5ml of acetonitrile was treated with N-butyl-ethyl-amine (2.000 g, 20 mmol) and heated at reflux for 0.5 hours. The mixture was cooled, diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to give 2.271 g (100%) of title compound as a light-brown oil. ^{1}H NMR ($CDCl_3$) δ 0.93 (t, 3H), 1.13 (t, 3H), 1.22-1.36 (m, 2H), 1.45-1.6 (m, 2H), 2.43 (s, 3H), 3.25-3.60 (m, 4H), 6.15 (s, 1H) ppm.

B. N-Butyl-N-ethyl-2-methyl-N'-(2,4,6-trimethylphenyl)-pyrimidine-4,6-diamine

A mixture of butyl-(6-chloro-2-methyl-pyrimidin-4-yl)-ethylamine (1.006 g, 4.42 mmol), and 2,4,6-trimethylaniline (3ml) was heated at reflux overnight. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give 2.862 g of a brown oil. The oil was purified through silica gel column chromatography to give 981 mg (68%) of title compound as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 0.80 (t, 3H), 1.1-1.3 (m, 2H), 1.3-1.5 (m, 2H), 2.17 (s, 6H), 2.27 (s, 3H), 2.41 (s, 3H), 3.2 (m, 2H), 3.36 (m, 2H), 4.66 (s, 1H), 6.90 (s, 2H) ppm.

Example 3

A. Butyl-(6-chloro-2-methyl-5-ethyl-pyrimidin-4-yl)-ethylamine

A mixture of 2-methyl-5-ethyl-4,6-dichloro-pyrimidine (1.009 g, 5.28 mmol) in 5 ml of acetonitrile was treated with triethylamine (0.571 g, 5.65 mmol) and N-butyl-ethyl-amine (0.540 g, 5.31 mmol) and heated at reflux overnight. The mixture was diluted with water and dilute hydrogen chloride, and extracted with ethyl acetate. The organic layer was neutralized with saturated potassium carbonate and washed with brine, dried and concentrated to give 1.193 g of yellow oil which was purified through silica gel column chromatography to give 1.157 g (86%) of title compound as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3H), 1.13 (t, 3H), 1.18 (t, 3H), 1.1-1.33 (m, 2H), 1.4-1.6 (m, 2h), 2.41 (s, 3H), 2.62 (q, 2H), 3.25-3.48 (m, 4H) ppm.

B. N-Butyl-N-ethyl-2-methyl-5-ethyl-N'-(2,4,6-trimethylphenyl)-pyrimidine-4,6-diamine

A mixture of butyl-(6-chloro-2-methyl-5-ethyl-pyrimidin-4-yl)-ethylamine (200 mg, 0.78 mmol) and 2,4,6-trimethylaniline (0.963 g, 7.1 mmol) was heated at reflux for 4 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with saturated potassium carbonate and brine, dried and concentrated to give a dark oil. The oil was distilled to give 579 mg of the dark oil which was then purified through silica gel column chromatography using chloroform as eluent to give the title compound as a brown oil. ^{1}H NMR ($CDCl_3$) δ 0.93 (t, 3H), 1.14 (t, 3H), 1.1-1.4 (m, 4H), 1.45-1.60 (m, 2H), 2.17 (s, 6H), 2.30 (s, 3H), 2.33 (s, 3H), 3.2-3.4 (m, 4H), 6.90 (s, 2H) ppm.

Example 4

2-Methyl-5-nitro-N,N'-bis-(2,4,6-trimethylphenyl)-pyrimidine-4,6-diamine

A mixture of 2-methyl-5-nitro-4,6-dichloropyrimidine (0.513 g, 2.47 mmol) in 6 ml of acetonitrile was treated with 2,4,6-trimethylaniline (0.333 g, 2.46 mmol) and triethylamine (1 ml) and stirred at room temperature for 4 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to give 0.622 g of bright yellow solid. The solid was purified through silica gel column chromatography to give (6-chloro-2-methyl-5-nitro-pyrimidin-4-yl)-(2,4,6-trimethylphenyl) amine and the title compound. ^{1}H NMR ($CDCl_3$) for 6-(chloro-2-methyl-5-nitro-pyrimidin-4-yl)-(2,4,6-trimethylphenyl)amine δ 2.16 (s, 6H), 2.33 (s, 3H), 2.43 (s, 3H), 6.95 (s, 2H), 8.79 (s, 1H) ppm. ^{1}H NMR ($CDCl_3$) for 2-methyl-5-nitro-N,N'-bis-(2,4,6-trimethylphenyl)-pyrimidine-4,6-diamine: δ 2.11 (s, 3H), 2.22 (s, 12H), 2.33 (s, 3H), 6.96 (s, 4H), 10.44 (s, 2H) ppm.

Example 5

N-Butyl-N-ethyl-2-methyl-5-nitro-N'-(2,4,6-trimethylphenyl)-pyrimidine-4,6-diamine

A mixture of 6-(chloro-2-methyl-5-nitropyrimidin-4-yl)-(2,4,6-trimethyl-phenyl)amine (838 mg, 2.10 mmol) and N-ethyl-n-butyl-amine (555 mg, 5.48 mmol) in 15 ml acetonitrile was heated at reflux for 2 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to give 0.837 g of yellow oil. The solid was purified through silica gel column chromatography using 1:1 hexane to chloroform as eluent to give 753 mg of the title compound as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3H), 1.26 (t, 3H), 1.2-1.4 (m, 2H), 1.55-1.75 (m, 2H), 2.17 (s, 6H), 2.23 (s, 3H), 2.31 (s, 3H), 3.4-3.6 (m, 4H), 6.93 (s, 2H), 9.43 (s, 1H) ppm.

Example 6

The following compounds were prepared by a method analogous to that of Examples 3 or 5 starting with an appropriate amine and appropriate (6-chloro-2-methyl-5-substituted-pyrimidin-4-yl)-(2,4,6-trimethylphenyl)amine.

N-Propyl-N-ethyl-2-methyl-5-nitro-N'-(2,4,6-trimethylphenyl)-pyrimidine-4,6-diamine: ^{1}H NMR ($CDCl_3$) δ 0.93 (t, 3H), 1.26 (t, 3H). 1.6-1.8 (m, 2H), 2.17 (s, 6H), 2.23 (s, 3H). 2.31 (s, 3H), 3.4-3.55 (m, 4H), 6.93 (s, 2H), 9.41 (s, 1H) ppm.

N-Butyl-5-ethyl-2-methyl-N'-(2,4,6-trimethylphenyl)-pyrimidine-4,6-diamine: ^{1}H NMR ($CDCl_3$) δ 0.98 (t, 3H), 1.12 (t, 3H), 1.3-1.5 (m, 2H), 1.5-1.7 (m, 2H), 2.17 (s, 3H), 2.30 (s, 3H), 3.4-3.5 (m, 2H), 4.30 (brs, 1H), 5.65 (brs, 1H), 6.91 (s, 2H) ppm.

5,N-Diethyl-2-methyl-N'-(2,4,6-trimethylphenyl)-pyrimidine-4,6-diamine: ^{1}H NMR ($CDCl_3$) δ 1.09 (t, 3H), 1.25 (t, 3H), 2.17 (s, 3H), 2.30 (s, 3H), 2.31 (s, 3H), 3.4-3.6 (m, 2H), 4.35 (brs, 1H), 6.90 (s, 2H) ppm.

Example 7

N-Butyl-N-ethyl-2-methyl-N'-(2,4,6-trimethylphenyl)-pyrimidine-4,5,6-triamine

A mixture of N-butyl-N-ethyl-2-methyl-5-nitro-N'-(2,4,6-trimethylphenyl)-pyrimidine-4,6-diamine (242 mg, 0.65 mmol) and platinum oxide (35 mg) in 50 ml ethanol was hydrogenated at 40 psi for 24 hours. The mixture was filtered through celite and concentrated to dryness to give 217 mg of yellow oil. The oil was purified through silica gel column chromatography to give 135 mg (61%) of title compound. ^{1}H NMR ($CDCl_3$) δ 0.91 (t, 3H), 1.09 (t, 3H), 1.2-1.4 (m, 2H), 1.4-1.6 (m, 2H), 2.18 (s, 6H), 2.30 (s, 3H), 2.34 (s, 3H), 3.0 (brs, 2H), 3.1-3.3 (m, 4H), 5.89 (s, 1H), 6.92 (s, 2H) ppm.

Example 8

The following compounds were prepared by the method of Example 7 by hydrogenation of the corresponding 5-nitro derivatives.

N-Propyl-N-ethyl-2-methyl-N'-(2,4,6-trimethylphenyl)-pyrimidine-4,5,6-triamine: ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H), 1.09 (t, 3H), 1.45-1.60 (m, 2H), 2.18 (s, 6H), 2.30 (s, 3H), 2.34 (s, 3H), 3.80 (brs, 2H), 3.1-3.30 (m, 4H), 5.95 (brs, 1H), 6.92 (s, 2H) ppm.

2-Methyl-N,N'-bis-(2,4,6-trimethylphenyl)-pyrimidine-4,5,6-triamine:

^{1}H NMR ($CDCl_3$) δ 2.04 (brs, 2H), 2.21 (s, 12H), 2.22 (s, 3H), 2.30 (s, 6H), 6.30 (s, 2H), 6.92 (s, 4H) ppm.

Example 9

6-(Ethyl-propyl-amino-2-methyl-9-(2,4,6-trimethylphenyl)-7,9-dihydropurin-8-one

A mixture of N-propyl-N-ethyl-2-methyl-N'-(2,4,6-trimethyl-phenyl)-pyrimidine-4,5,6-triamine (120 mg, 0.35 mmol) and triethylamine (87 mg, 0.86 mmol) in 5 ml of dry tetrahydrofuran was treated with triphosgene (41 mg, 0.14 mmol) at 0°C. Precipitate formed immediately and the reaction mixture was warmed to room temperature. After stirring for 30 minutes the mixture was filtered. The filtrate was concentrated to dryness to give 125 mg (100%) of titl compound of a greenish color. ^{1}H NMR ($CDCl_3$) δ 0.90

(t, 3H), 1.21 (t, 3H), 1.65 (m, 2H), 2.10 (s, 6H), 2.34 (s, 3H), 2.39 (s, 3H), 3.48 (dd, 2H), 3.58 (q, 2H), 6.99 (s, 2H), 9.63 (s, 1H) ppm.

Example 10

6-(Ethyl-propyl-amino)-2,7-dimethyl-9-(2,4,6-trimethylphenyl)-7,9-dihydropurin-8-one

A mixture of the title compound of Example 9 (54 mg, 0.15 mmol) in 3 ml of dry tetrahydrofuran was treated with sodium hydride (9 mg, 0.23 mmol, 60% in oil) at room temperature. The mixture was then treated with 0.02 ml of methyl iodide and stirred at room temperature overnight. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give 60 mg of brown oil. The oil was purified through silica gel column chromatography using chloroform as eluent to give 56 mg of the title compound as a yellow oil which crystallized on standing. ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 3H), 1.17 (t, 3H), 1.63 (m, 2H), 2.06 (s, 6H), 2.33 (s, 3H), 2.46 (s, 3H), 3.32 (dd, 2H), 3.40 (q, 2H), 3.63 (s, 3H), 7.00 (s, 2H) ppm.

Example 11

The following compounds were prepared by the method of Example 10 by reacting the title compound of Example 9 with an appropriate alkyl iodide.

7-Ethyl-6-(ethyl-propyl-amino)-2-methyl-9-(2,4,6-trimethylphenyl)-7,9-dihydropurin-8-one:

^{1}H NMR ($CDCl_3$) δ 0.92 (t, 3H), 1.14 (t, 3H), 1.23 (m, 3H), 1.58 (m, 2H), 2.04 (s, 6H), 2.31 (s, 3H), 2.45 (s, 3H), 3.32 (dd, 2H), 3.36 (q, 2H), 4.08 (q, 2H), 7.00 (s, 2H) ppm.

6-(Ethyl-propyl-amino)-2-methyl-7-propyl-9-(2,4,6-trimethylphenyl)-7,9-dihydropurin-8-one:

^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3H), 0.90 (t, 3H), 1.15 (t, 3H), 1.5-12.8 (m, 4H), 2.05 (s, 6H), 2.33 (s, 3H), 2.47 (s, 3H), 3.32 (dd, 2H), 3.38 (q, 2H), 4.01 (q, 2H), 7.00 (s, 2H) ppm.

Example 12

[4-Chloro-2-methyl-6-(2,4,6-trimethylphenylamino)-pyrimidin-5-yl]-acetic acid ethyl ester

A mixture of (2-methyl-4,6-dichloro-pyrimidine-5-yl)-acetic acid ethyl ester (1.470 g, 5.9 mmol) and 2,4,6-trimethylaniline (2.56 ml, 17.7 mmol), in 15 ml of dimethylsulfoxide was heated at 120°C overnight and 138°C for 5 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was

washed with brine, dried and concentrated to give a brown oil. The oil was purified through silica gel column chromatography to give 1.070 g (52%) of the title compound as a tan solid. ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 3H), 2.14 (s, 6H), 2.32 (s, 3H), 2.37 (s, 3H), 3.79 (s, 2H), 4.23 (q, 2H), 7.00 (s, 2H), 7.02 (s, 1H) ppm.

Example 13

A. 4-Chloro-2-methyl-7-(2,4,6-trimethylphenylamino)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one

A mixture of the title compound of Example 12 (960 mg, 2.76 mmol) and p-toluene sulfonic acid (105 mg, 0.55 mmol) in 10 ml of toluene was heated at reflux under Dean-Stark trap for 8 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to give 800 mg of a brown mass which was purified through silica gel column chromatography to give 348 mg (42%) of the title compound as a yellow powder. ^{1}H NMR ($CDCl_3$) δ 2.06 (s, 6H), 2.34 (s, 3H), 2.56 (s, 3H), 3.75 (s, 2H), 7.02 (s, 2H) ppm.

B. 4-(1-Hydroxymethyl-propylamino)-2-methyl-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-d]pyrimidine-6-one

A mixture of the compound prepared under A (168 mg, 0.557 mmol) and (S)-2-amino-butanol (0.27 ml, 2.78 mmol) in 5 ml of dimethyl sulfoxide was heated at 145°C for 5 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to give an oil. The oil was purified through silica gel column chromatography, followed by recrystallization with diethyl ether to give 166 mg of the title compound as a grey solid.

^{1}H NMR ($CDCl_3$) δ 1.25 (t, 6H), 1.5-1.8 (m, 2H), 2.07 (s, 6H), 2.31 (s, 3H), 2.37 (s, 3H), 3.50 (s, 2H), 3.4-3.9 (m, 2H), 4.0 (m, 1H), 4.* (d, 1H), 7.00 (s, 2H) ppm.

Example 14

4-Diethylamino-2-methyl-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one

The title compound was prepared by the method of Example 13B with diethylamine instead of (S)-2-amino-butanol. ^{1}H NMR ($CDCl_3$) δ 1.02 (t, 3H), 2.08 (s, 6H), 2.31 (s, 3H), 2.37 (s, 3H), 3.55 (q, 4H), 3.85 (s, 2H), 6.95 (s, 2H) ppm.

Example 15

A. 4-Chloro-2,5,5-trimethyl-7-(2,4,6-trimethylphenylamino)-5,7-dihydro-pyrrolo[2,3-d]pyrmidin-6-one and 4-Chloro-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one

A mixture of 4-chloro-2-methyl-7-(2,4,6-trimethylphenylamino)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one (93 mg, 0.31 mmol) and sodium hydride (14 mg, 0.34 mmol, 60% in oil) in tetrahydrofuran (THF) was stirred for 5 minutes, then treated with an excess of methyl iodide and stirred for 1 hour. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to give an oil. The oil was purified through silica gel column chromatography to give 32 mg of 4-chloro-2,5,5-trimethyl-7-(2,4,6-trimethylphenyl-amino)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one and 64 mg of 4-chloro-2,5-dimethyl-7-(2,4,6-trimethyl)-phenylamino)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one.

^{1}H NMR ($CDCl_3$) (4-chloro-2,5,5-trimethyl-7-(2,4,6-trimethylphenylamino)-5,7-dihydropyrrolo[2,3-d]pyrimidin-6-one) δ 1.61 (s, 6H), 2.03 (s, 6H), 2.32 (s, 3H), 2.53 (s, 3H), 7.00 (s, 2H) ppm.

^{1}H NMR ($CDCl_3$) (4-chloro-2,5-dimethyl-7-(2,4,6-trimethylphenylamino)-5,7-dihydropyrrolo[2,3-d]pyrimidin-6-one) δ 1.65 (d, 2H), 2.03 (s, 3H), 2.06 (s, 3H), 2.34 (s, 3H), 2.56 (s, 3H), 3.72 (q, 1H), 7.00 (s, 2H) ppm.

B. 4-(1-hydroxymethylpropylamino)-2,5,5-trimethyl-7-(2,4,6-trimethylphenyl)-5,7-dihydropyrrolo[2,3-d]pyrimidin-6-one

The title compound was prepared by the method of Example 13B from 4-chloro-2,5,5-trimethyl-7-(2,4,6-trimethylphenylamino)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one) and (S)-2-amino-butanol in dimethylsulfoxide at 140°C. ^{1}H NMR ($CDCl_3$) δ 1.02 (t, 3H), 1.53 (s, 6H), 1.5-1.8 (m, 2H), 2.04 (s, 6H), 2.32 (s, 3H), 2.38 (s, 3H), 3.6-3.9 (m, 2H), 4.0 (m, 1H), 4.5 (d, 1H), 5.25 (brs, 1H), 7.00 (s, 2H) ppm.

Example 16

5-Hydroxy-4-(1-hydroxymethylpropylamino)-2,5-dimethyl-7-(2,4,6-trimethyl-phenyl)-5,7-dihydropyrrolo[2,3-d]pyrimidin-6-one

The title compound was prepared by the method of Example 13B from 4-chloro-2,5-dimethyl-7-(2,4,6-trimethylphenylamino)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one) and (S)-2-amino-butanol in dimethylsulfoxide (DMSO) at 140°C. Two diastereomers were obtained. The spectra for both diastereomers are shown below:

One isomer: ^{1}H NMR ($CDCl_3$) δ 1.03 (t, 3H), 1.55-1.75 (m, 2H), 1.77 (s, 3H), 2.05 (s, 3H), 2.07 (s, 3H), 2.32 (s, 3H), 2.37 (s, 3H), 3.55-3.85 (m, 2H), 4.0 (m, 1H), 5.1 (d, 1H), 5.3 (brs, 1H), 7.00 (s, 2H) ppm.

The other isomer: ^{1}H NMR ($CDCl_3$) δ 1.03 (t, 3H), 1.55-1.75 (m, 2H), 1.73 (s, 3H), 2.02 (s, 3H), 2.05 (s, 3H), 2.32 (s, 3H), 2.36 (s, 3H), 3.58 (dd, 1H), 3.77 (dd, 1H), 4.1 (m, 1H), 5.03 (d, 1H), 7.00 (s, 2H) ppm.

Example 17

5-Methoxy-4-(butyl-ethyl-amino)-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one

5-Hydroxy-4-(butyl-ethyl-amino)-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one was prepared by the method analogous to that of Example 16 starting with 4-chloro-2,5-dimethyl-7-(2,4,6-trimethylphenylamino)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one) and N-butyl-ethyl-amine in DMSO at 140°C. Methylation of 5-hydroxy-4-(butyl-ethyl-amino)-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one with sodium hydride and methyl iodide using the method of Example 10 provides the title compound. ^{1}H NMR ($CDCl_3$) δ 6.97 (d, 2H), 3.5-4.0 (m, 4H), 3.23 (s, 3H), 2.34 (s, 3H), 2.32 (s, 3H), 2.12 (s, 3H), 2.03 (s, 3H), 1.69 (s, 3H), 1.6-1.8 (m, 2H), 1.3-1.5 (m, 2H), 1.24 (t, 3H), 0.99 (t, 3H) ppm.

Example 18

4-(Butyl-ethyl-amino)-2-methyl-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one

The title compound was prepared by the method analogous to that of Example 13 (B) starting with 4-chloro-2-methyl-7-(2,4,6-trimethylphenylamino)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one) and N-butyl-ethyl-amine in DMSO at 135°C for 2.5 hours to give an oil. ^{1}H NMR ($CDCl_3$) 7.00 (s, 2H), 3.85 (s, 2H), 3.62 (q, 2H), 3.53 (t, 2H), 2.35 (s, 3H), 2.32 (s, 3H), 2.10 (s, 3H), 1.55-1.70 (m, 2H), 1.35-1.50 (m, 2H), 1.25 (t, 3H), 1.00 (t, 3H) ppm.

Example 19

4-(Butyl-ethyl-amino)-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one

A solution of 4-(butyl-ethyl-amino)-2-methyl-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one (285 mg, 0.78 mmol) in 5 ml of dry THF was treated with lithium bis(trimethylsilyl)amid (1.05 mmol) at -78°C and stirred for 5

minutes. The mixture was quenched with methyl iodide (0.054 ml, 0.858 mmol) at -78°C. After stirring for 10 minutes, the mixture was warmed to 0°C and stirred at that temperature for 20 minutes. The mixture was quenched with saturated ammonium chloride and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to give a purple form. The form was purified through silica gel column chromatography to give 4-(butyl-ethyl-amino)-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one (120 mg) as a purple glass, 4-(butyl-ethyl-amino)-2,5,5-trimethyl-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one (35 mg) as a purple glass, and 98 mg of a mixture of the two components as a purple glass.

^{1}H NMR ($CDCl_3$) (4-(butyl-ethyl-amino)-2,5-dimethy-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one) δ 6.96 (s, 2H), 3.7-3.9 (m, 2H), 3.51 (q, 1H), 3.15-3.4 (m, 2H), 2.34 (s, 3H), 2.30 (s, 3H), 2.08 (s, 3H), 2.05 (s, 3H), 1.53 (d, 3H), 1.5-1.65 (m, 2H), 1.3-1.4 (m, 2H), 1.17 (t, 3H), 0.95 (t, 3H) ppm.

^{1}H NMR ($CDCl_3$) (4-(butyl-ethyl-amino)-2,5,5-trimethy-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one) δ 6.98 (s, 2H), 3.45 (q, 2H), 3.34 (t, 2H), 2.34 (s, 3H), 2.33 (s, 3H), 2.06 (s, 6H), 1.55-1.7 (m, 2H), 1.3-1.45 (m, 2H), 1.23 (t, 3H), 0.99 (t, 3H) ppm.

Example 20

Butyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl]-ethylamine

A solution of (4-butyl-ethyl-amino)-2,5-dimethyl-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one) (111 mg, 0.292 mmol) in dry THF was treated with lithium aluminum hydride at room temperature. The resulting mixture was heated at reflux for 5 hours. After standard work-up, 97 mg of crude material as an oil was obtained. The oil was purified through a chromatotron using 10% ethyl acetate in hexane as eluent to give butyl-[2,5-dimethyl-7-(2,4,6-trimethylphenyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl]-ethylamine as a clear pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 6.91 (d, 2H), 3.7-3.9 (m, 2H), 3.2-3.4 (m, 4H), 2.5 (q, 1H), 2.28 (s, 6H), 2.22 (s, 3H), 2.05 (s, 3H), 1.5-1.7 (m, 2H), 1.3-1.5 (m, 5H), 1.17 (t, 3H), 0.97 (t, 3H) ppm. High MS ($C_{23}H_{34}N_4$) calc. 366.2776, found 366.27622.

Example 21

4-(Butyl-ethyl-amino)-2,5,5-trimethyl-7-(2,4,6-trimethylphenyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-6-ol

The title compound was prepared by the method of Example 20 starting from (4-(butyl-ethyl-amino)-2,5,5-trimethyl-7-(2,4,6-trimethylphenyl)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one) to give a pale yellow solid, mp 142-145°C; ^{1}H NMR ($CDCl_3$) δ 6.95 (d, 2H), 4.90 (s, 1H), 3.1-3.4 (m, 4H), 2.4 (brs, 1H), 2.33 (s, 3H), 2.31 (s, 3H), 2.21 (s, 3H), 2.17 (s, 3H), 1.50 (s, 3H), 1.45 (s, 3H), 1.25-1.60 (m, 4H), 1.11 (t, 3H), 0.93 (t, 3H) ppm.

Example 22

Butyl-ethyl-[6-methoxy-2,5,5-trimethyl-7-(2,4,6-trimethylphenyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-4-yl]-amine

To a solution of 4-(butyl-ethyl-amino)-2,5,5-trimethyl-7-(2,4,6-trimethylphenyl)-6,7-dihydro-5H-pyrrolo[2,3-d]pyrimidin-6-ol] (20 mg, 0.05 mmol) in 1 ml of dry THF was treated with sodium hydride (60% in oil, 4 mg, 0.1 mmol) and then methyl iodide (0.3 ml) was added at room temperature. After stirring at room temperature for 2.5 hours, the mixture was quenched with saturated ammonium chloride and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to give 26 mg of crude material. After silica gel column purification with 10% ethyl acetate in hexane, 19 mg of a colorless oil of the title compound was obtained. ^{1}H NMR ($CDCl_3$) δ 6.92 (s, 1H), 6.89 (s, 1H), 4.48 (s, 1H), 3.1-3.3 (m, 4H), 3.11 (s, 3H), 2.32 (s, 3H), 2.28 (s, 3H), 2.20 (s, 3H), 2.19 (s, 3H), 1.45 (s, 3H), 1.44 (s, 3H), 1.4-1.52 (m, 2H), 1.2-1.4 (m, 2H), 1.10 (t, 3H), 0.90 (t, 3H) ppm.

Example 23

4-(Butyl-ethyl-amino)-2-methyl-7-(2,4,6-trimethylphenyl)-7H-pyrrolo[2,3-d]pyrimidine-5,6-dione

To a solution of 4-(butyl-ethyl-amino)-2-methyl-7-(2,4,6-trimethyphenyl)-5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one (76 mg, 0.207 mmol), $POCl_3$ (0.039 ml, 0.415 mmol), triethylamine (0.059 ml), and dimethylamine (1 ml) in 2 ml acetonitrile was heated at reflux for 1 hour. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give a brown form (105 mg). After silica gel column chromatography, the title compound was isolated as a yellow glass (10 mg). ^{1}H NMR ($CDCl_3$) δ 7.00 (s, 2H), 3.95-4.15 (m, 2H), 3.65-3.85 (m,

2H), 2.38 (s, 3H), 2.32 (s, 3H), 2.10 (s, 6H), 1.55-1.75 (m, 2H), 1.35-1.55 (m, 2H), 1.25 (t, 3H), 1.00 (t, 3H) ppm.

Example 24

N-Butyl-N-ethyl-2,5,N'-trimethyl-N'-(2,4,6-trimethylphenyl)-pyrimidine-4,6-diamine

A mixture of (6-chloro-2,5-dimethyl-pyrimidin-4-yl)-methyl-(2,4,6-trimethylphenyl)-amine (200 mg) and N-butyl-ethylamine (0.3 ml) in 1 ml of DMSO was heated in oil bath of 160°C for 15 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was separated, dried and concentrated to give the crude material. After silica gel column purification using chloroform as eluent, the title compound was obtained as an oil. ^{1}H NMR ($CDCl_3$) δ 6.83 (s, 2H), 3.22 (s, 3H), 3.12 (m, 4H), 2.44 (s, 3H), 2.26 (s, 3H), 2.01 (s, 6H), 1.35-1.42 (m, 2H), 1.1-1.25(m, 2H), 1.00 (t, 3H), 0.90 (t, 3H) ppm.

Example 25

[2,5-Dimethyl-6-(tetrahydrofuran-3-yloxy)-pyrimidin-4-yl]-(2,4,6-trimethylphenyl)-amine

A mixture of 3-hydroxy-tetrahydrofuran (0.5 ml) and sodium hydride (60% in oil, 53 mg, 1.33 mmol) in dry THF was stirred at room temperature for 5 minutes, (6-chloro-2,5-dimethyl-pyrimidin-4-yl)-(2,4,6-trimethylphenyl)-amine (107 mg, 0.388 mmol) was added. The mixture was heated at reflux for 15 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was separated, dried and concentrated to give a yellow oil. The oil was purified through silica gel column chromatography using 20% ethyl acetate in hexane as eluent to give 48 mg of the title compound as off-white crystals, mp 126-128°C. ^{1}H NMR ($CDCl_3$) δ 6.89 (s, 2H), 5.60 (brs, 2H), 3.8-4.0 (m, 4H), 2.27 (s, 6H), 2.13 (s, 6H), 2.1-2.25 (m, 2H), 1.93 (s, 3H) ppm.

Example 26

2-(S)-[2,5-Dimethyl-6-(2,4,6-trimethylphenoxy)-pyrimidin-4-ylamino]-butan-ol

A mixture of 4-chloro-2,5-dimethyl-6-(2,4,6-trimethylphenyoxy)-pyrimidine (30 mg) and 2-(S)-amino-1-butanol (0.5 ml) in 0.5 ml of DMSO was heated at 130°C for 4 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was separated, dried and concentrated to give a crude material. The crude residue was purified through silica gel column chromatography to give 24 mg of the title compound as white crystals. High MS for ($C_{19}H_{27}N_3O_2$) calc. 329.2103, found 329.21249; IR(KBr) 3400, 2940, 1580 cm-1; ^{1}H NMR ($CDCl_3$) δ 6.841 (s, 2H), 5.72 (brs,

1H), 4.45 (d, 1H), 3.82-3.96 (m, 1H), 3.72-3.9 (m, 1H), 3.5-3.6 (m, 1H), 2.27 (s, 3H), 2.21 (s, 3H), 2.08 (s, 3H), 2.02 (s, 6H), 1.4-1.7 (m, 2H), 1.03 (t, 3H) ppm.

Example 27

4-(1-Ethyl-propoxy)-2,5-dimethyl-6-(2,4,6-trimethylphenoxy)-pyrimidine

A mixture of 3-pentanol (0.3 ml) and sodium hydride (60% in oil, 32 mg, 0.81 mmol) in DMSO was stirred at room temperature for 5 minutes. 4-Chloro-2,5-dimethyl-6-(2,4,6-trimethylphenyoxy)-pyrimidine (150 mg, 0.54 mmol) was added and the resulting mixture was heated at 150°C for 5 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was separated, dried and concentrated to give a beige solid. The solid was purified through silica gel column chromatography using 20% chloroform in hexane as eluent to give the title compound as white crystals, mp 93.5-95.5°C. ^{1}H NMR ($CDCl_3$) δ 6.85 (s, 2H), 5.11 (t, 1H), 2.27 (s, 3H), 2.26 (s, 3H), 2.11 (s, 3H), 2.03 (s, 6H), 1.68 (p, 4H), 0.92 (t, 6H) ppm.

Example 28

[[6-(Butyl-N-ethylamino)-2-methylpyrimidin-4-yl]-(2,4,6-trimethylphenyl)-amino]-acetic acid ethyl ester

A mixture of [(6-chloro-2-methylpyrimidin-4-yl)-(2,4,6-trimethylpheny)-amino]-acetic acid ethyl ester (85 mg, 0.244 mmol) and N-butyl-ethylamine (0.17 ml, 1.1 mmol) in 4 ml DMSO was heated at 135°C for 15 hours. An additional 1 ml of N-butyl-ethylamine was added and the reaction was heated at that temperature for an additional 15 hours (tlc showed no starting material). The mixture was quenched with water and extracted with ethyl acetate. The organic layer was separated, dried and concentrated to give 123 mg of a light amber oil. The oil was purified through silica gel chromatotron using 5% ethyl acetate in hexane as eluent to give 92 mg (91%) of the title compound as a white glass. ^{1}H NMR ($CDCl_3$) δ 6.94 (s, 2H), 4.69 (s, 1H), 4.23 (s, 2H), 4.22 (q, 2H), 3.35 (q, 2H), 3.15 (t, 2H), 2.36 (s, 3H), 2.31 (s, 3H), 2.21 (s, 6H), 1.3-1.5 (m, 2H), 1.34 (t, 3H), 1.1-1.3 (m, 2H), 1.01 (t, 3H), 0.80 (t, 3H) ppm.

Example 29

4-(1-Ethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine

To a solution of 3-pentanol (0.2 ml, 0.5205 mol) in DMSO (1 ml) was added 60% sodium hydride in oil (30 mg) in a portionwise. After stirring at room temperature for 5 min, a solution of 4-chloro-2,5-dimethyl-6-(2,4,6-trimethylphenoxy)-pyridine (98 mg) in 0.5 ml of dry THF was added and th resulting mixture was heated at 130°C for

5 hours. The mixtur was quenched with water and extracted with ethyl acetat . The organic layer was separated, dried and concentrated to give a yellow solid. The solid was purified through silica gel column chromatography using 20% chloroform in hexane to chloroform as eluent to give 7 mg of the title compound as white crystals, mp 72.5-74°C. ^{1}H NMR ($CDCl_3$) δ 6.84 (s, 2H), 6.26 (s, 1H), 4.16 (m, 1H), 2.27 (s, 3H), 2.17 (s, 6H), 2.04 (s, 6H), 1.69 (m, 4H), 0.95 (t, 6H) ppm.

The mesylate salt of 4-(1-ethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine was prepared by addition of 1 equivalent of methanesulfonic acid in ethyl acetate. The white crystals formed from ethyl acetate. Mp 117-119°C.

Example 30

[6-(Butyl-ethyl-amino)-2,5-dimethylpyrimidin-4-yl]-(2,4,6-trimethylphenyl)-acetonitrile

A solution of mesitylacetonitrile (66 mg, 0.41 mmol) in 1 ml of DMSO was treated with NaH (60% in oil, 20 mg, 0.50 mmol) and stirred at room temperature for 20 minutes, butyl-(6-chloro-2,5-dimethylpyrimidin-4-yl)-ethylamine (100 mg, 0.414 mmol) was added and the resulting mixture was heated at 130°C for 15 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was separated, dried and concentrated to give 160 mg of brown oil. The oil was purified through silica gel column chromatography using 5% ethyl acetate in hexane as eluent to give the title compound as a brown oil. ^{1}H NMR ($CDCl_3$) δ 6.83 (s, 2H), 5.49 (s, ^{1}H), 3.2-3.4 (m, 2H), 3.0-3.2 (m, 2H), 2.51 (s, 3H), 2.24 (s, 3H), 2.21 (s, 6H), 1.66 (s, 3H), 1.35-1.50 (m, 2H), 1.1-1.3 (m, 2H), 1.05 (t, 3H), 0.84 (t, 3H) ppm.

Example 31

2-[6-(1-Ethyl-propoxy)-2,5-dimethylpyrimidin-4-yl]-2-(2,4,6-trimethylphenyl)-propionitrile

To a solution of 3-pentanol (140 mg, 1.59 mmol) in 2 ml of dry THF was added sodium hydride (60% in oil, 38 mg) and the mixture was stirred at room temperature for 5minutes. 2-(6-Chloro-2,5-dimethylpyrimidin-4-yl)-2-(2,4,6-trimethylphenyl)-propionitrile (100 mg, 0.319 mmol) was added to the reaction mixture, and the resulting mixture was heated at reflux for 4 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was separated, dried and concentrated to give a brown oil (170 mg). The residue was purified through chromatotron using 20% ethyl acetate in hexane as eluent to give a mixture of two isomers as a yellow glass form and both having a M+ of 365 from GC/Ms. ^{1}H NMR ($CDCl_3$) δ 6.8 and 6.76 (s, 2H), 4.08 and 3.96 (m, ^{1}H), 3.25 and 3.22 (s, 3H), 2.36 and 2.30 (s, 3H), 2.21, 2.20 and 2.06 (s, total of 9H), 1.5-1.7 (m, 4H), 1.04 (s, 3H), 0.96 and 0.90 (t, 3H) ppm.

Example 32

4-(1-Ethyl-propoxy)-2,5-dimethyl-6-(2,4,6-trimethyl-benzyl)-pyrimidine

The title compound was prepared by the method analogous to that in Example 32 starting with 4-Chloro-2,5-dimethyl-6-(2,4,6-trimethyl-benzyl)-pyrimidine and 3-pentanol. White crystals, mp. 82-84°C.

The title compounds of Example 33-39 were prepared by a method analogous to that of Example 27, starting with the appropriate 4-chloro-2-methyl-5-substituted 6-substituted-phenoxy)-pyrimidine and 3-pentanol.

Example 33

4-(2,4-Dimethyl-phenoxy)-6-(1-ethyl-propoxy)-2,5-dimethyl-pyrimidine

^{1}H NMR ($CDCl_3$) δ 6.8-7.0 (m, 3H), 5.13 (m, 1H), 2.30 (s, 6H), 2.10 (s, 3H), 2.09 (s, 3H), 1.68 (m, 4H), 0.92 (t, 6H) ppm.

Example 34

4-(2,6-Dimethyl-phenoxy)-6-(1-ethyl-propoxy)-2,5-dimethyl-pyrimidine

^{1}H NMR ($CDCl_3$) δ 7.04 (m, 3H), 5.12 (m, 1H), 2.25 (s, 3H), 2.13 (s, 3H), 2.07 (s, 6H), 1.66 (m, 4H), 0.92 (t, 6H) ppm.

Example 35

4-(1-Ethyl-propoxy)-2-methyl-6-(2,4,6-trimethyl-phenoxy)-pyrimidine-5-carbonitrile

mp 128-130°C, ^{1}H NMR ($CDCl_3$) δ 6.8 (s, 2H), 5.18 (m, 1H), 2.30 (s, 3H), 2.21 (s,3H), 2.00 (s,6H), 1.4-1.58 (m, 4H), 0.90 (t, 6H) ppm.

Example 36

5-tert-Butyl-4-(1-ethyl-propoxy)-2-methyl-6-(2,4,6-trimethyl-phenoxy)-pyrimidine

^{1}H NMR ($CDCl_3$) δ 6.85 (s, 2H), 5.25 (m, 1H), 2.29 (s, 3H), 2.20 (s, 3H), 2.03 (s, 6H), 1.65-1.80 (m, 4H), 1.52 (s, 9H), 0.90 (t, 6H) ppm.

Example 37

4-(1-Ethyl-propoxy)-5-isopropyl-2-methyl-6-(2,4,6-trimethyl-phenoxy)-pyrimidine

^{1}H NMR ($CDCl_3$) δ 6.85 (s, 2H), 5.17 (m, 1H), 3.50 (m, 1H), 2.27 (s, 3H), 2.23 (s, 3H), 2.03 (s, 6H), 1.69 (m, 4H), 1.33 (s, 3H), 1.31 (s, 3H), 0.92 (t, 6H) ppm.

Example 38

5-Bromo-4-(1-ethyl-propoxy)-2-methyl-6-(2,4,6-trimethyl-phenoxy)-pyrimidine

^{1}H NMR ($CDCl_3$) δ 6.86 (s, 2H), 5.16 (m, 1H), 2.29 (s, 3H), 2.28 (s, 3H), 2.06 (s, 6H), 1.65-1.80 (m, 4H), 1.52 (s, 9H), 0.95 (t, 6H) ppm.

Example 39

5-Chloro-4-(1-ethyl-propoxy)-2-methyl-6-(2,4,6-trimethyl-phenoxy)-pyrimidine

^{1}H NMR ($CDCl_3$) δ 6.86 (s, 2H), 5.16 (m, 1H), 2.28 (s, 3H), 2.27 (s, 3H), 2.06 (s, 6H), 1.65-1.80 (m, 4H), 1.52 (s, 9H), 0.94 (t, 6H) ppm.

The title compounds of Examples 40-41 were prepared by a method analogous to that described in Example 24, starting from 4-chloro-2,5-dimethyl-6-(2,4,6-trimethylphenoxy)-pyrimidine and the appropriate amine.

Example 40

[2,5-Dimethyl-6-(2,4,6-trimethyl-phenoxy)-pyrimidin-4-yl](1-ethyl-propyl)-amine

^{1}H NMR ($CDCl_3$) δ 6.84 (s, 2H), 4.10 (m, 2H, NH and CH), 2.27 (s, 3H), 2.21 (s, 3H), 2.04 (s, 9H), 1.3-1.6 (m, 4H), 0.91 (t, 6H) ppm.

Example 41

Butyl-[2,5-dimethyl-6-(2,4,6-trimethyl-phenoxy)-pyrimidin-4-yl]-ethyl-amine

^{1}H NMR ($CDCl_3$) δ 6.87 (s, 2H), 3.76 (m, 2H), 3.68 (t, 2H), 2.73 (s, 3H), 2.28 (s, 6H), 1.99 (s, 6H), 1.5-1.7 (m, 4H), 1.27 (t, 3H), 0.94 (t, 3H) ppm.

The title compounds of Examples 42-54 were prepared by a method analogous to that described in Example 29, starting with the appropriate 4-chloro-2-methyl-6-(substituted phenoxy or thiophenoxy)-pyridine and the appropriate alcohol.

Example 42

2-(4-Bromo-2,6-dimethyl-phenoxy)-4-(1-ethyl-prpoxy)-3,6-dimethyl-pyridine

^{1}H NMR ($CDCl_3$) δ 7.18 (s, 2H), 6.30 (s, 1H), 4.22 (m, 1H), 2.20 (s, 6H), 2.05 (s, 6H), 1.73 (m, 4H), 1.00 (t, 6H) ppm.

Example 43

2-(4-Chloro-2,6-dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine

^{1}H NMR ($CDCl_3$) δ 7.05 (s, 2H), 6.31 (s, 1H), 4.20 (m, 1H), 2.20 (s, 6H), 2.08 (s, 6H), 1.73 (m, 4H), 0.99 (t, 6H) ppm.

Example 44

3-Ethyl-4-(1-ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-pyridine

^{1}H NMR ($CDCl_3$) δ 6.85 (s, 2H), 6.26 (s, 1H), 4.18 (m, 1H), 2.73(q,2H), 2.28 (s, 3H), 2.17 (s, 3H), 2.05 (s, 6H), (m, 4H), 1.18 (t, 3H), 0.96 (t, 6H) ppm.

Example 45

4-(1-ethyl-propenyloxy)-3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine (A mixture of cis and trans isomers)

^{1}H NMR ($CDCl_3$) δ 6.85 (s, 2H), 6.30 (s, 0.3H), 6.21 (s, 0.7H), 5.10 (m, 0.7H), 4.95 (m, 0.3H), 2.27 (s, 3H), 2.24 (s, 2.1H), 2.19 (s, 0.9H), 2.14 (s, 3H), 2.05 (s, 6H), 1.65 (d, 0.9H), 1.50 (d, 2.1H), 1.08 (t, 1.8H), 1.05 (t, 4.2H) ppm.

Example 46

Methanesulfonic acid salt of 4-(1-ethyl-propoxy)-2,3,5-trimethyl-6-(2,4,6-trimethyl-phenoxy)-pyridine

Mp 58-60°C. ^{1}H NMR ($CDCl_3$) δ 6.90 (s, 2H), 4.20 (m, 1H), 2.70 (s, 3H), 2.61 (s, 3H), 2.28 (s, 3H), 2.16 (s, 3H), 2.08 (s, 6H), 1.5-1.8 (m, 4H), 0.96 (t, 6H) ppm.

Example 47

4-(1-Ethyl-propoxy)-6-methyl-2-(2,4,6-trimethyl-phenoxy)-nicotinic acid methyl ester

^{1}H NMR ($CDCl_3$) δ 6.84 (s, 2H), 6.39 (s, 1H), 5.04 (m, 1H), 3.85 (s, 3H), 2.27 (s, 3H), 2.23 (s, 3H), 2.05 (s, 6H), 1.5-1.7 (m, 4H), 0.95 (s, 6H) ppm.

Example 48

4-(1-Ethyl-propoxy)-2-methyl-6-(2,4,6-trimethyl-phenoxy)-pyridine

^{1}H NMR ($CDCl_3$) δ 6.90 (s, 2H), 6.34 (d, J-2Hz,1H), 5.70 (d, J=2Hz,1H), 4.05 (m, 1H), 2.40 (s, 3H), 2.30 (s, 3H), 2.11 (s, 6H), 1.62 (m, 4H), 0.89 (t, 6H) ppm.

Example 49

3,6-Dimethyl-4-(tetrahydro-furan-3-yloxy)-2-(2,4,6-trimethyl-phenoxy)-pyridine

^{1}H NMR ($CDCl_3$) δ 6.88 (s, 2H), 6.25 (s, 1H), 4.99 (m, 1H), 3.9-4.1 (m, 4H), 2.31 (s, 3H), 2.23 (s, 3H), 2.20 (s, 3H), 2.1-2.3 (m, 2H), 2.07 (s, 6H) ppm.

Example 50

4-(1-Methoxymethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine

^{1}H NMR ($CDCl_3$) δ 6.88 (s, 2H), 6.38 (s, 1H), 4.42 (m, 1H), 3.5-3.7 (m, 2H), 3.42 (s, 3H), 2.31 (s, 3H), 2.21 (s, 6H), 2.07 (s, 6H), 1.7-1.85 (m, 2H), 1.02 (t, 3H) ppm.

Example 51

3-[3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yloxy]-pentan-2-ol

^{1}H NMR ($CDCl_3$) δ 6.88 (s, 2H), 6.34 (s, 1H), 4.25-4.45 (m, 1H0, 3.6-3.8 (m, ^{1}H), 2.30 (s, 3H)2.21 (s, 3H), 2.20 (s, 3H), 2.06 (s, 6H), 1.2-1.4 (m, 5H0, 1.07 (t, 3H) ppm.

Example 52

4-sec-Butoxy-3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridine

^{1}H NMR ($CDCl_3$) δ 6.88 (s, 2H), 6.31 (s, 1H), 4.35 (m, 1H), 2.30 (s, 3H), 2.21 (s, 3H), 2.19 (s, 3H), 2.07 (s, 6H0, 1.7-1.9 (m, 2H), 1.34 (d, 3H), 1.01 (t, 3H) ppm.

Example 53

2-(2,4-Dimethyl-phenylsulfanyl)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine

Golden oil. ^{1}H NMR ($CDCl_3$) δ 7.19 (d, j=8Hz,1H0, 7.06 (s, 1H), 6.94 (d, J=8Hz,1H), 6.42 (s, 1H), 4.19 (m, 1H), 2.34 (s, 3H), 2.33 (s, 3H), 2.32 (s, 3H), 2.18 (s, 3H), 1.69 (m, 4H), 0.95 (t, 6H) ppm.

Example 54

4-(1-Ethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethyl-phenylsulfanyl)-pyridine

^{1}H NMR ($CDCl_3$) δ 6.97 (s, 2H), 6.30 (s, 1H), 4.15 (m, 1H), 2.35 (s, 6H), 2.30 (s, 3H), 2.23 (s, 3H), 2.20 (s, 3H), 1.68 (m, 4H), 0.95 (t, 6H) ppm.

Example 55

2-(4-Ethyl2,6-dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine

To a solution of 2.5 N n-BuLi in hexane (0.47 ml, 1.18 mmol) in 5ml of dry THF was added a solution of 2-(4-bromo-2,6-dimethyl-phenoxy)-4-(1-ethyl-prpoxy)-3,6-dimethyl-pyridine (465 mg, 1.18 mmol) in 5 ml of dry THF at -78°C. After stirring at that temperature for 5 min, an excess of ethyl iodide (0.4 ml) was added and the resulting mixture was stirred at -78°C for 30 min, then at 0°C for 15 min. The mixture was quenched with saturated ammonium chloride and extracted with ethyl acetate. The organic layer was dried and concentrated to give a light brown oil The oil was puriified through silica gel column chromatography using chloroform as eluent to give 260 mg of the title compound as white solid. ^{1}H NMR ($CDCl_3$) δ 6.90 (s, 2H), 6.38 (s, 1H), 4.20 (m, 1H), 2.61(q,2H), 2.24 (s, 3H), 2.21 (s, 3H), 2.10 (s, 6H), 1.70 (m, 4H), 1.30 (t, 3H), 0.98 (t, 6H) ppm.

The title compounds of Examples 56-62 were prepared by a method analogous to that described in Example 55, starting from n-BuLi and 2-(4-bromo-2,6-dimethyl-phenoxy)-4-(1-ethyl-prpoxy)-3,6-dimethyl-pyridine, followed by quenching with an appropriate electrophile.

Example 56

4-[4-(1-Ethyl-propoxy)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-benzaldehyde

^{1}H NMR ($CDCl_3$) δ 9.94 (s, 1H), 7.61 (s, 2H), 6.32 (s, 1H), 4.20 (m, 1H), 2.21 (s, 3H), 2.16 (s, 9H)1.70 (m, 4H), 0.98 (t, 6H) ppm.

Example 57

2-(2,6-Dimethyl-4-propyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine

^{1}H NMR ($CDCl_3$) δ 6.88 (s, 2H), 6.30 (s, 1H), 4.20 (m, 1H), 2.54(dd,2H), 2.22 (s, 3H), 2.20 (s, 3H), 2.09 (s, 6H), 1.6-1.8 (m, 6H), 0.9-1.1 (m, 9H) ppm.

Example 58

2-(2,6-Dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine

^{1}H NMR ($CDCl_3$) δ 7.06 (m, 3H), 6.30 (s, 1H), 4.20 (m, 1H), 2.21 (s, 6H), 2.11 (s, 6H), 1.73 (m, 4H), 0.99 (t, 6H) ppm.

Example 59

2{4-[4-(1-Ethyl-propoxy)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-phenyl}-propan-2-ol

^{1}H NMR ($CDCl_3$) δ 7.15 (s, 2H), 6.25 (s, 1H), 4.20 (m, 1H), 2.20 (s, 3H), 2.19 (s, 3H), 2.10 (s, 6H), 1.85 (brs, ^{1}H),1.70 (m, 4H), 1.60 (s, 6H), 0.95 (t, 6H) ppm.

Example 60

4-(1-Ethyl-propoxy)-2-(4-iodo-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridine

^{1}H NMR ($CDCl_3$) δ 7.39 (s, 2H), 6.30 (s, 1H), 4.19 (m, 1H), 2.20 (s, 3H), 2.18 (s, 3H), 2.05 (s, 6H), 1.72 (m, 4H), 0.98 (t, 6H) ppm.

Example 61

4-[4-(1-Ethyl-propoxy)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-phenol

^{1}H NMR ($CDCl_3$) δ 7.85 (brs, 1H), 6.36 (s, 1H), 6.24 (s, 2H), 4.24 (m, 1H), 2.39 (s, 3H), 2.20 (s, 3H), 2.02 (s, 6H), 1.74 (m, 4H), 1.00 (t, 6H) ppm.

Example 62

1-{4-[4-(1-Ethyl-propoxy)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-phenyl}-pyrrolidin-2-one

^{1}H NMR ($CDCl_3$) δ 7.30 (s, 2H), 6.30 (s, 1H), 4.20 (m, 1H), 3.88 (t, 2H), 2.61 (t, 2H) ppm.

Example 63

{4-[4-(1-Ethyl-propoxy)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-phenyl}-methanol

A mixture of 4-[4-(1-ethyl-propoxy)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-benzaldehyde (114 mg, 0.41 mmol) and sodium borohydride (63 mg, 1.6 mmol) in 3 ml of methanol was stirred at room temperature for 2 hours. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give yellow oil. The oil was purified through silica gel using chloroform as eluent to give 70 mg of the title compound as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.04 (s, 2H), 6.32 (s, 1H), 4.55 (s, 2H), 4.21 (m, 1H), 2.30 (brs, 1H), 2.22 (s, 3H), 2.21 (s, 3H), 2.12 (s, 6H), 1.73 (m, 4H), 0.91 (t, 6H) ppm.

Example 64

4-(1-Ethyl-propoxy)-2-(4-methoxy-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridine

To a solution of 4-[4-(1-ethyl-propoxy)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-phenol (40 mg, 0.12mmol) in 3 ml of dry THF was added 10 mg of 60% sodium hydride in oil at room temperature. After stirring for 5 min, 0.3 ml of methyl iodide was added and the resulting mixtur was stirred at room temperature ov rnight. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give a yellow solid. The solid was purified through silica gel column

chromatography using hexane to 1:1 chloroform:hexane as eluent to yield 20 mg of the title compound as yellow solid. ^{1}H NMR ($CDCl_3$) δ 6.66 (s, 2H), 6.28 (s, 1H), 4.20 (m, 1H), 3.79 (s, 3H), 2.20 (s, 3H), 2.19 (s, 3H0, 2.08 (s, 6H), 1.71 (m, 4H), 0.97 (t, 6H) ppm.

Example 65

4-(1-Ethyl-propoxy)-2-(4-isopropoxy-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridine

To a solution of 4-[4-(1-ethyl-propoxy)-3,6-dimethyl-pyridin-2-yloxy]-3,5-dimethyl-phenol (58 mg, 0.176mmol) in 3 ml of dry THF was added triphenylphosphine (70 mg, 0.264mmol) and isopropanol (60 mg, 0.22 mmol). The resulting mixture was stirred at room temperature for 5 min, diethyl azodicarboxylate (46 mg, 0.264 mmol) was added. The mixture was stirred at room temperature overnight. An additional 20 mg of diethyl azodicarboxylate was added and the mixture was stirred for an additional 4 hours. The mixture was quenched with water and extracted with methylene chloride. The organic layer was dried and concentrated to give an oil. The oil residue was purified through silica gel column chromatography using 1:1 hexane:chloroform to 1:2 hexane: chloroform as eluent to give 38 mg (58%) of the title compound as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 6.60 (s, 2H), 6.28 (s, 1H), 4.50 (m, 1H), 4.18 (m, 1H), 2.20 (s, 3H), 2.19 (s, 3H), 2.079s,6H), 1.71 (m, 4H), 1.34 (d, 6H), 0.98 (t, 6H) ppm.

The title compounds of Examples 66-67 were prepared by a method analogous to that described in Example 64, starting with an appropriate pyridine-3,5-dimethylphenol or pyridine-3,5-dimethyl-phenyl methanol with a base, followed by quenching with an appropriate alkyl halide.

Example 66

2-(4-Ethoxy-2,6-dimethyl-phenoxy)-4-(1-ethyl-propoxy)-3,6-dimethyl-pyridine

^{1}H NMR ($CDCl_3$) δ 6.60 (s, 2H), 6.28 (s, 1H), 4.19 (m, 1H), 3.99(q,2H), 2.19 (s, 3H), 2.18 (s, 3H), 2.07 (s, 6H), 1.74 (m, 4H), 1.40 (t, 3H), 0.97 (t, 6H) ppm.

Example 67

4-(1-Ethyl-propoxy)-2-(4-methoxymethyl-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridine

Mp 58-60°C. ^{1}H NMR ($CDCl_3$) δ 7.05 (s, 2H), 6.30 (s, 1H), 4.41 (s, 2H), 4.19 (m, 1H), 3.42 (s, 3H), 2.21 (s, 3H), 2.18 (s, 3H), 2.11 (s, 6H), 1.72 (m, 4H), 0.98 (s, 6H) ppm.

Example 68

[3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)--pyridin-4-yl]-ethyl-amine

A mixture of 4-chloro-3,6-dimethyl-2-(2,4,6-trimethylphenoxy)-pyridine (1.330 g, 4.822 mmol) and 20 ml of ethyl amine in 13 ml of 1-methyl-2-pyrrolidinone was heated

at 150°C at 250 psi overnight in a pressure reactor. The reaction was heated an additional 24 hours at 175°C and 300 psi. The reaction mixture cooled to room temperature and diluted with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give a brown oil. The oil residue was purified through silica gel column chromatography using chloroform to 2% methanol in chloroform as eluent to give 0.820 g (60%) of the title compound as a white solid, mp 115-116°C.

^{1}H NMR ($CDCl_3$) δ 6.87 (s, 2H), 6.11 (s, 1H), 3.85 (t, 1H), 3.24 (m, 2H), 2.30 (s, 3H), 2.17 (s, 3H), 2.13 (s, 3H), 2.08 (s, 6H), 1.32 (t, 3H) ppm.

The title compounds of Examples 69-71 were prepared by the method analogous to that described in Example 68 starting with an appropriate 4-chloro-2-substituted phenoxy-pyridine and an appropriate amine.

Example 69

[3,6-Dimethyl-2-(2,4,6-trimethyl-phenylsulfanyl)-pyridin-4-yl]-(1-ethyl-propyl)-amine

Mp 108-110°C. ^{1}H NMR ($CDCl_3$) δ 6.95 (s, 2H), 6.09 (s, 1H), 3.63 (d, 1H), 3.28 (m, 1H), 2.36 (s, 6H), 2.30 (s, 3H), 2.17 (s, 3H), 2.11 (s, 3H), 1.4-1.75 (m, 4H0, 0.93 (t, 6H) ppm. The hydrogen chloride salt, mp 148-150°C; ^{1}H NMR ($CDCl_3$) δ 6.95 (s, 2H), 6.30 (s, 1H), 5.75 (d, ^{1}H), 3.38 (m, 1H), 2.69 (s, 3H), 2.33 (s, 6H), 2.28 (s, 3H0, 2.02 (s, 3H), 1.72 (m, 4H), 0.93 (t, 6H) ppm.

Example 70

2-(4-Chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-ethyl-amine; white solid

^{1}H NMR ($CDCl_3$) δ 7.04 (s, 2H), 6.13 (s, 1H), 3.88 (t, 1H), 3.24 (m, 2H), 2.17 (s, 3H), 2.17 (s, 3H), 2.08 (s, 6H), 1.32 (t, 3H) ppm.

Example 71

[3,6-dimethyl-2-(2,4,6-trimethyl-phenylsulfanyl)-pyridin-4-yl]-ethyl-amine

Tan crystals, mp 114-116°C. ^{1}H NMR ($CDCl_3$) δ 6.94 (s, 2H), 6.12 (s, 1H), 3.76 (t, 1H), 3.21 (m, 2H), 2.35 (s, 6H), 2.30 (s, 3H), 2.19 (s, 3H), 2.10 (s, 3H), 1.29 (t, 3H) ppm.

Example 72

[3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-ethyl-propyl-amine

To a solution of [3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)--pyridin-4-yl]-ethyl-amine (7.00 g, 24.6 mmol) in 100 ml of dry THF was added 1.0 M lithium bis(trimethylsilyl)amide in hexane (32 ml, 32 mmol) at -78°C. After stirring at that temperature for 10 min, the reaction mixtur was treated with iodopropane (13 ml, 125 mmol) at -70°C. After stirring at that temp rature for 20 min, the dry ice bath was removed and the reaction mixture was stirred at room temperature for 3 hours. The

reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give an oil. The oil residue was purified through silica gel column chromatography using 1:1 chloroform:hexane to chloroform as eluent to give 5.04 g (62.5%) of [3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-ethyl-propyl-amine as yellow solid; ^{1}H NMR ($CDCl_3$) δ 6.88 (s, 2H), 6.41 (s, 1H), 3.11(q,2H), 3.03(dd,2H), 2.30 (s, 3H), 2.25 (s, 3H), 2.19 (s, 3H), 2.07 (s, 6H), 1.55 (m, 2H), 1.08 (t, 3H), 0.90 (t, 3H) ppm. The corresponding HCl salt, white crystals; mp167-169°C; ^{1}H NMR (MeOH-d4) δ 7.00 (s, 2H), 6.75 (s, 1H), 3.54(q,2H), 3.43 (t, 2H), 2.35 (s, 3H), 2.31 (s, 3H), 2.27 (s, 3H), 2.08 (s, 6H), 1.69 (m, 2H), 1.25 (t, 3H0, 0.94 (t, 3H) ppm;

The title compounds of Examples 73-79 were prepared by the method analogous to that described in Example 72 starting with an appropriate 2-(substituted phenoxy or thiophenoxy)-pyridin-4-yl-ethyl amine and a base (lithium bis(trimethylsilyl)amide or lithium diisopropylamide), followed by quenching with an appropriate alkyl halide.

Example 73

[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)--pyridin-4-yl]-diethyl-amine

^{1}H NMR ($CDCl_3$) δ 6.87 (s, 2H), 6.40 (s, 1H), 3.10(q,4H), 2.30 (s, 3H), 2.24 (s, 3H), 2.19 (s, 3H), 2.06 (s, 6H), 1.08 (t, 6H) ppm. The HCl salt, white crystals, mp 180-181°C; ^{1}H NMR (CD_3OD) δ 7.01 (s, 2H), 6.78 (s, 1H), 3.58(q,4H), 2.38 (s, 3H), 2.32 (s, 6H), 2.10 (s, 6H), 1.28 (t, 6H) ppm.

Example 74

[3,6-Dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-ethyl-methyl-amine

^{1}H NMR ($CDCl_3$) δ 6.86 (s, 2H), 6.38 (s, 1H), 3.05(q,2H), 2.75 (s, 3H), 2.29 (s, 3H), 2.25 (s, 3H), 2.18 (s, 3H), 2.06 (s, 6H), 1.18 (t, 3H) ppm. The HCl salt, mp 173-174°C.

Example 75

Butyl-[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-ethyl-amine

^{1}H NMR ($CDCl_3$) δ 6.88 (s, 2H), 6.41 (s, 1H), 3.0-3.3 (m, 4H), 2.31 (s, 3H), 2.25 (s, 3H), 2.19 (s, 3H), 2.08 (s, 6H), 1.3-1.6 (m, 4H), 1.09 (t, 3H), 0.93 (t, 3H) ppm.

Example 76

Butyl-[2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-ethyl-amine

^{1}H NMR ($CDCl_3$) δ 7.03 (s, 2H), 6.39 (s, 1H), 3.09(q,2H), 3.01(dd,2H), 2.21 (s, 3H), 2.16 (s, 3H), 2.05 (s, 6H), 1.4-1.6 (m, 2H), 1.25-1.40 (m, 2H), 1.06 (t, 3H), 0.87 (t, 3H) ppm. The HCl salt, mp 177-178°C; ^{1}H NMR(DMSO-d6) δ 7.20 (s, 2H), 6.74 (s, 1H),